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 5th, 2021 1:00 - 5:00 PM
Remote Meeting via Zoom Platform
MEETING AGENDA

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

I. CALL TO ORDER

1:00 PM	A. Roll Call & Introductions	R. Citron (OSU)
	B. Approval of Agenda	R. Citron (OSU)
	C. Conflict of Interest Declaration	R. Citron (OSU)
	D. Approval of Minutes	R. Citron (OSU)
	E. Department Update	T. Douglass (OHA)
	F. Legislative Update	T. Douglass (OHA)
1:20 PM	II. CONSENT AGENDA TOPICS	S. Ramirez (Chair)
	A. CMS Annual Report	
	B. Quarterly Utilization Reports	
	C. Oncology Prior Authorization Updates	
	1. Public Comment	

III. DUR ACTIVITIES

1:25 PM	A. ProDUR Report	L. Starkweather (Gainwell)
	B. RetroDUR Report	D. Engen (OSU)
	C. Oregon State Drug Review	K. Sentena (OSU)
	1. Antidepressant Review	
	2. Bipolar Disorder: Resources for Primary Care Providers	

IV. PREFERRED DRUG LIST NEW BUSINESS

1:45 PM	A. SGLT-2 Inhibitors Class Update	K. Sentena (OSU)
	1. Class Update/Prior Authorization Criteria	
	2. Public Comment	
	3. Discussion of Clinical Recommendations to OHA	
2:00 PM	B. Amondys 45™ (casmisersen) New Drug Evaluation	S. Servid (OSU)
	1. New Drug Evaluation/Prior Authorization Criteria	
	2. Public Comment	
	3. Discussion of Clinical Recommendations to OHA	

2:15 PM	C. Benlysta® (belimumab) Prior Authorization Update 1. Prior Authorization Update 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	D. Moretz (OSU)
2:30 PM	D. Other Dyslipidemia Drugs Class Update and New Drug Evaluation 1. Class Update/Prior Authorization Criteria 2. Evkeeza™ (evinacumab-dgnb) New Drug Evaluation 3. Public Comment 4. Discussion of Clinical Recommendations to OHA	M. Herink (OSU)
2:50 PM	E. Overactive Bladder Class Update and New Drug Evaluation 1. Class Update 2. Gemtesa® (vibegron) New Drug Evaluation 3. Public Comment 4. Discussion of Clinical Recommendations to OHA	K. Sentena (OSU)
3:05 PM	BREAK	
3:20 PM	F. Asthma Biologics DERP Summary 1. DERP Summary/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	D. Moretz (OSU)
3:40 PM	G. Phosphate Binders Literature Scan 1. Literature Scan/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	D. Moretz (OSU)
3:50 PM	H. HIV Class Update and New Drug Evaluation 1. DERP Report and Class Update 2. Cabenuva™ (cabotegravir/rilpivirine) and Vocabria™ (cabotegravir) New Drug Evaluations 3. Public Comment 4. Discussion of Clinical Recommendations to OHA	S. Fletcher (OSU) A. Gibler (OSU)
4:20 PM	V. EXECUTIVE SESSION	
4:50 PM	VI. RECONVENE for PUBLIC RECOMMENDATIONS	
	VII. ADJOURN	

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Name	Title	Profession	Location	Term Expiration
Mark Helm, MD, MBA, FAAP	Physician	Pediatrician	Salem	December 2021
Russell Huffman, DNP, PMHNP	Public	Mental Health Nurse Practitioner	Salem	December 2021
Jim Rickards, MD, MBA	Physician	Radiologist / Medical Director	McMinnville	December 2021
Cathy Zehrung, RPh	Pharmacist	Pharmacy Manager	Silverton	December 2021
Patrick DeMartino, MD	Physician	Pediatrician	Portland	December 2022
Cat Livingston, MD, MPH	Physician	Medical Director, Health Share	Portland	December 2022
Stacy Ramirez, PharmD	Pharmacist	Ambulatory Care Pharmacist	Corvallis	December 2022
Tim Langford, PharmD, BCPS, USPHS	Pharmacist	Pharmacy Director, Klamath Tribes	Klamath Falls	December 2023
Caryn Mickelson, PharmD	Pharmacist	Pharmacy Director, Coquille Indian Tribe	Coos Bay	December 2023
Robin Moody, MPH	Public	Executive Director, Oregon Health Forum	Portland	December 2023
William Origer, MD, FAAFP	Physician	Residency Faculty	Albany	December 2023

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Thursday, June 3, 2021 1:00 - 5:00 PM

Via Zoom webinar

MEETING MINUTES

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

Members Present: Stacy Ramirez, PharmD; William Origer, MD, FAAFP; Mark Helm, MD, MBA, FAAP; Russell Huffman, DNP, PMHNP; Patrick DeMartino, MD; Cat Livingston, MD, MPH; Tim Langford, PharmD, BCPS, USPHS; Robin Moody, MPH; Caryn Mickelson, PharmD, Cathy Zehrung, PharmD

Staff Present: Jennifer Bowen, Admin; Roger Citron, RPh; David Engen, PharmD; Sara Fletcher, PharmD; Richard Holsapple, RPh; Deanna Moretz, PharmD; Sarah Servid, PharmD; Megan Herink, PharmD; Dee Weston, JD; Brandon Wells; Amanda Parrish, LCSW; Kyle Hamilton.

Audience: Andrea Willcuts, Takeda; Andrew Yu, Novartis; Bill McDougall, Biogen; Brandie Feger, Advanced Health; Brandon Yip, Sanofi-Genzyme; **Carrie Johnson, PharmD, Amgen**; Chi Kohlhoff, Viela Bio; Chris Yates, Merck; Craig Sexton, GSK; Cyreatha Bryant, RPh, Gainwell Technologies; Dennis Schaffner, Sanofi-Genzyme; Gregg Rasmussen, Vertex Pharmaceuticals; Jason Tessmer, Novo Nordisk; **Jennifer Shear, PharmD, Teva**; Joel Rios, Gainwell Technologies; Kalpesh Patel, Gainwell Technologies; Kara Tyler, Kite Pharma; Katie Scheelar, Moda/EOCCO; Lindsey Walter, Novartis; **Lisa Allen, Vertex Pharmaceuticals**; Lisa Dunn, Amgen; **Lynda Finch, PhD, Biogen**; **Margaret Olmon, PharmD, AbbVie**; Mark Kantor, AllCare CCO; Matt Worthy, OHSU; Timothy McFerrin, Alkermes; Melissa Snider, Gilead Sciences; Michael Foster, BMS; Mike Donabedian, Sarepta Therapeutics; Nancy Mahler, Oncopeptides; Rebecca Rubin, BioCryst; Rick Frees, Vertex; Robert Pearce, Teva; **Shirley Quach, Novartis**; Sophia Yun, Janssen; **Steve Hall, Genentech**; Tina Shriner, AbbVie; **Wendy Bibeau, BMS**.

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

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I. CALL TO ORDER

A. Roll Call & Introductions
   a. Called to order at approx. 1:08 p.m., introductions by staff and committee.
B. Approval of Agenda
C. Conflict of Interest Declaration
D. Approval of April 2021 Minutes presented by Mr. Citron
   ACTION: Motion to approve, 2nd, all in favor
E. Department Update
F. Legislative Update

II. CONSENT AGENDA TOPICS

A. Quarterly Utilization Reports
B. Colony Stimulating Factors Literature Scan
C. Oncology Prior Authorization Updates
D. Orphan Drug Policy Updates
   ACTION: Motion to approve, 2nd, all in favor

III. DUR ACTIVITIES

A. ProDUR Report: Rich Holsapple, RPh
B. RetroDUR Report: Dave Engen, PharmD
C. Oregon State Drug Review: Kathy Sentena, PharmD
   a. Covid-19 Viral Testing
   b. 2019-2020 Food and Drug Administration Drug Safety Communications Update
   c. Coronavirus Disease-2019 Vaccine Update

IV. DUR OLD BUSINESS

A. **Antipsychotics in Young Children Safety Edit:** Sarah Servid, PharmD
   Recommendations:
   a. Implement a safety edit to ensure appropriate use of antipsychotics in children 5 years of age or less
   b. Implement a retrospective provider outreach program
   ACTION: Motion to approve, 2nd, all in favor

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V. PREFERRED DRUG LIST NEW BUSINESS

A. **Growth Hormone ADR & Prior Authorization (PA) Update:** Dave Engen, PharmD
Recommendation:
   a. Add somapacitan-beco to Growth Hormone PDL class, designate non-preferred, and restrict use for OHP-covered conditions
   b. Update to PA criteria to align with HERC coverage guidance and FDA-approved indications

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

B. **Hereditary Angioedema Class Update (NDE):** Sarah Servid**,** PharmD
Recommendation:
   a. Update PA criteria to include berotralstat
   b. No changes to the PDL based on clinical evidence
   c. Evaluate costs in executive session

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

C. **Multiple Sclerosis Drug Class Update & New Drug Evaluation for Kesimpta (Ofatumumab) and Ponvory (Ponesimod) (NDE):** Deanna Moretz, PharmD
Recommendations:
   a. Update PA criteria to apply to ofatumumab for both PAD and POS pharmacy claims
   b. Add ponesimod tablets to the Oral MS Drug PA criteria and update as proposed
   c. Evaluate costs in executive session

Public Comment: Wendy Bibeau, BMS; Lynda Finch, Biogen; Steve Hall, Genentech; Shirley Quach, Novartis

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

D. **Focused Heart Failure Update and New Drug Evaluation for Entresto (Sacubitril/Valsartan) and Verquvo (Vericiguat) (NDE):** Megan Herink, PharmD
Recommendations:
   a. Rename the "ACEIs, ARBs and DRIs" PDL class to "Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)" and include sacubitril/valsartan
   b. Update PA criteria for sacubitril/valsartan to include expanded FDA indications
   c. Require PA for vericiguat to ensure appropriate use in patients on goal directed therapy with advanced symptomatic HFrEF
   d. Evaluate costs in executive session

Public Comment: Shirley Quach, Novartis

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

E. **Platelet Inhibitor Class Update:** Kathy Sentena, PharmD
Recommendations:
   a. Update PA criteria to include new indications for ticagrelor

b. No changes to the PDL based on the evidence identified since the last review
c. Evaluate costs in executive session

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

VI. DUR NEW BUSINESS

A. **Migraine Prophylaxis Drug Use Evaluation (DUE):** Rebekah Bartholomew, PGY2 Resident; Megan Herink, PharmD; Sara Fletcher, PharmD
Recommendation:
a. No policy changes for triptan therapy are recommended at this time
b. Consider provider education to increase migraine prophylaxis use in patients taking chronic triptans
c. No PA criteria changes for CGRP antagonists recommended at this time
Public Comment: Jennifer Shear, Teva; Carrie Johnson, Amgen; Margaret Olmon, Abbvie
ACTION: Motion to approve, 2nd, all in favor

B. **Prior Authorization Criteria Update, Cystic Fibrosis:** Megan Herink, PharmD
Recommendation:
a. Remove manual review by medical director consistent with FDA labeling and standard of care from PA criteria for use of LUM/IVA in patients less than 12 years of age
b. Add a link to FDA labeling in the PA criteria to ensure all approved CFTR mutations are current
Public Comment: Lisa Allen, Vertex
ACTION: Motion to approve, 2nd, all in favor

VII. EXECUTIVE SESSION

Members Present: Stacy Ramirez, PharmD; William Origer, MD, FAAFP; Mark Helm, MD, MBA, FAAP; Russell Huffman, DNP, PMHNP; Patrick DeMartino, MD; Cat Livingston, MD, MPH; Tim Langford, PharmD, BCPS, USPHS; Caryn Mickelson, PharmD; Robin Moody, MPH

Staff Present: Jennifer Bowen, Admin; Roger Citron, RPh; David Engen, PharmD; Sara Fletcher, PharmD; Megan Herink, PharmD; Richard Holsapple, RPh; Deanna Moretz, PharmD; Sarah Servid, PharmD; Dee Weston, JD; Brandon Wells; Amanda Parrish, LCSW

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VIII. RECONVENE for PUBLIC RECOMMENDATIONS

A. **Colony Stimulating Factors Literature Scan:**
Recommendation: Make Nyvepria preferred and Neulasta non-preferred on the PDL

B. **Hereditary Angioedema:**
Recommendation: No changes to the PDL are recommended

C. **Multiple Sclerosis Class Update:**
Recommendation: Maintain non-preferred status for Kesimpta and Ponvory on the PDL

D. **Focused Heart Failure Class Update:**
Recommendation: Make Entresto non-preferred on the PDL

E. **Platelet Inhibitors:**
Recommendation: Make Prasugrel preferred on the PDL and remove from PA criteria

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

IX. ADJOURN

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Pharmacy Utilization Summary Report: January 2020 - December 2020

Eligibility	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Avg Monthly
Total Members (FFS & Encounter)	994,279	996,305	1,000,312	1,026,262	1,039,871	1,052,702	1,065,127	1,078,611	1,091,643	1,105,304	1,124,250	1,142,287	1,059,746
FFS Members	99,615	99,252	99,928	109,012	94,359	89,482	92,036	97,318	96,060	99,759	110,699	110,136	99,805
OHP Basic with Medicare	8,622	8,495	7,620	7,613	7,275	7,121	7,235	7,333	7,140	7,395	8,031	7,925	7,650
OHP Basic without Medicare	11,882	11,860	11,739	11,470	11,412	11,281	11,469	11,624	11,493	11,546	11,692	11,422	11,574
ACA	79,111	78,897	80,569	89,929	75,672	71,080	73,332	78,361	77,427	80,818	90,976	90,789	80,580
Encounter Members	894,664	897,053	900,384	917,250	945,512	963,220	973,091	981,293	995,583	1,005,545	1,013,551	1,032,151	959,941
OHP Basic with Medicare	69,949	70,261	71,185	71,584	72,135	72,516	72,537	72,713	73,520	74,103	74,533	75,527	72,547
OHP Basic without Medicare	62,920	62,837	62,961	63,059	62,873	62,810	62,587	64,059	65,009	65,428	65,582	66,083	63,851
ACA	761,795	763,955	766,238	782,607	810,504	827,894	837,967	844,521	857,054	866,014	873,436	890,541	823,544

Gross Cost Figures for Drugs	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	YTD Sum
Total Amount Paid (FFS & Encounter)	$88,396,317	$83,248,172	$97,494,147	$85,311,422	$81,874,648	$88,876,475	$90,463,426	$88,005,479	$88,739,349	$89,813,266	$86,029,055	$97,640,253	$1,065,892,010
Mental Health Carve-Out Drugs	$9,306,540	$8,616,232	$9,525,201	$9,049,995	$8,781,442	$9,436,194	$9,469,233	$9,175,034	$9,230,833	$9,454,791	$9,153,116	$10,072,546	$111,271,155
OHP Basic with Medicare	$36,750	$32,139	$31,845	$29,898	$29,851	$35,823	$32,866	$30,054	$38,156	$25,916	$26,636	$43,711	$393,644
OHP Basic without Medicare	$3,663,788	$3,321,973	$3,685,465	$3,476,896	$3,282,336	$3,641,928	$3,564,549	$3,591,355	$3,568,207	$3,691,725	$3,621,967	$3,904,199	$43,014,388
ACA	$5,550,377	$5,204,845	$5,749,623	$5,495,257	$5,418,162	$5,712,325	$5,830,087	$5,503,971	$5,577,767	$5,689,923	$5,449,648	$6,070,591	$67,252,578
FFS Physical Health Drugs	$3,092,718	$2,777,013	$3,059,523	$2,914,340	$2,526,476	$2,568,215	$2,559,160	$2,371,911	$2,482,795	$2,573,725	$2,299,729	$2,594,533	$31,820,138
OHP Basic with Medicare	$63,985	$53,501	$60,385	$52,596	$44,170	$51,909	$56,118	$48,377	$48,222	$47,671	$43,764	$48,622	$619,319
OHP Basic without Medicare	$1,114,870	$1,003,761	$1,087,280	$1,003,610	$909,086	$912,517	$870,473	$848,068	$867,035	$922,619	$775,653	$942,711	$11,257,683
ACA	$1,757,902	$1,580,202	$1,772,531	$1,738,757	$1,450,562	$1,461,367	$1,484,413	$1,348,897	$1,437,912	$1,490,604	$1,366,679	$1,473,174	$18,363,000
FFS Physician Administered Drugs	$1,502,348	$1,711,015	$1,577,427	$1,163,000	$1,163,639	$1,573,610	$1,576,519	$1,150,737	$1,102,552	$1,622,356	$1,165,952	$1,161,707	$16,470,863
OHP Basic with Medicare	$148,896	$117,855	$91,816	$121,999	$91,329	$116,592	$131,019	$95,607	$100,595	$82,924	$105,121	$111,654	$1,315,406
OHP Basic without Medicare	$341,068	$618,689	$313,089	$141,949	$365,022	$594,681	$495,740	$239,681	$241,384	$607,084	$325,718	$202,969	$4,487,074
ACA	$563,478	$518,370	$444,729	$485,948	$336,104	$366,902	$391,649	$374,398	$395,480	$461,764	$326,686	$453,124	$5,118,631
Encounter Physical Health Drugs	$58,036,206	$55,028,151	$65,507,973	$57,714,557	$54,870,499	$58,788,411	$60,906,270	$59,350,655	$60,164,312	$59,978,803	$58,143,439	$63,083,256	$711,572,532
OHP Basic with Medicare	$820,838	$703,088	$796,554	$666,873	$668,586	$729,965	$677,747	$652,716	$742,685	$755,860	$716,842	$761,381	$8,693,135
OHP Basic without Medicare	$14,121,857	$13,293,183	$15,363,627	$14,084,389	$13,192,372	$14,066,908	$14,035,375	$14,322,467	$14,661,801	$14,228,044	$14,409,968	$15,844,094	$171,624,085
ACA	$42,415,161	$40,421,294	$48,565,364	$42,373,801	$40,377,632	$43,413,770	$45,564,597	$43,749,895	$44,127,059	$44,257,742	$42,331,987	$45,806,987	$523,405,290
Encounter Physician Administered Drugs	$16,458,504	$15,115,762	$17,824,022	$14,469,531	$14,532,593	$16,510,046	$15,952,245	$15,957,142	$15,758,858	$16,183,591	$15,266,819	$20,728,210	$194,757,323
OHP Basic with Medicare	$599,300	$574,085	$653,004	$497,008	$593,456	$622,625	$647,344	$610,924	$684,398	$640,511	$617,154	$619,518	$7,359,327
OHP Basic without Medicare	$3,691,695	$3,703,737	$3,474,564	$3,562,982	$3,398,646	$3,570,317	$3,278,037	$3,423,035	$3,641,217	$3,685,623	$3,318,259	$7,227,921	$45,976,032
ACA	$11,733,803	$10,568,901	$13,456,702	$10,206,637	$10,233,560	$11,937,492	$11,662,850	$11,524,826	$10,966,443	$11,420,634	$10,801,974	$12,548,564	$137,062,387

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 22, 2021

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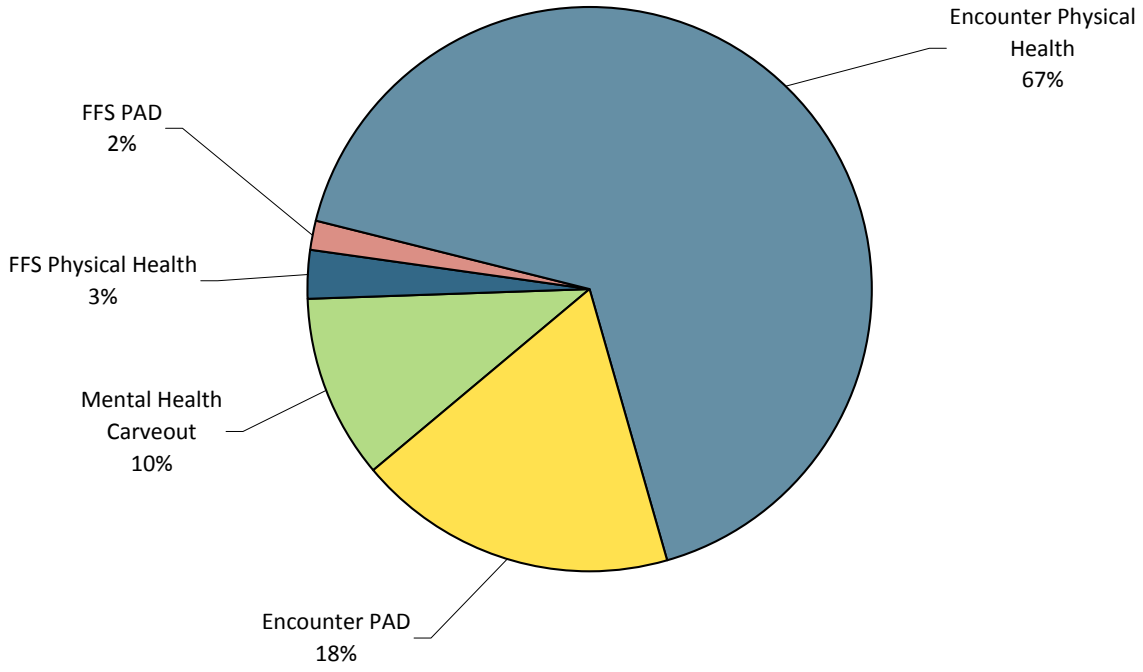
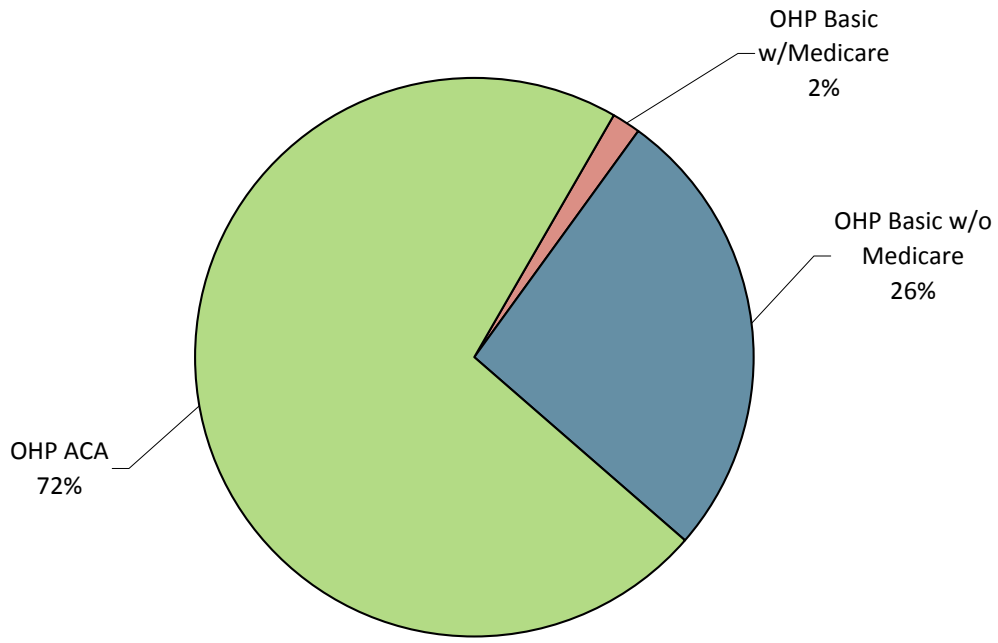
Pharmacy Utilization Summary Report: January 2020 - December 2020

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 22, 2021

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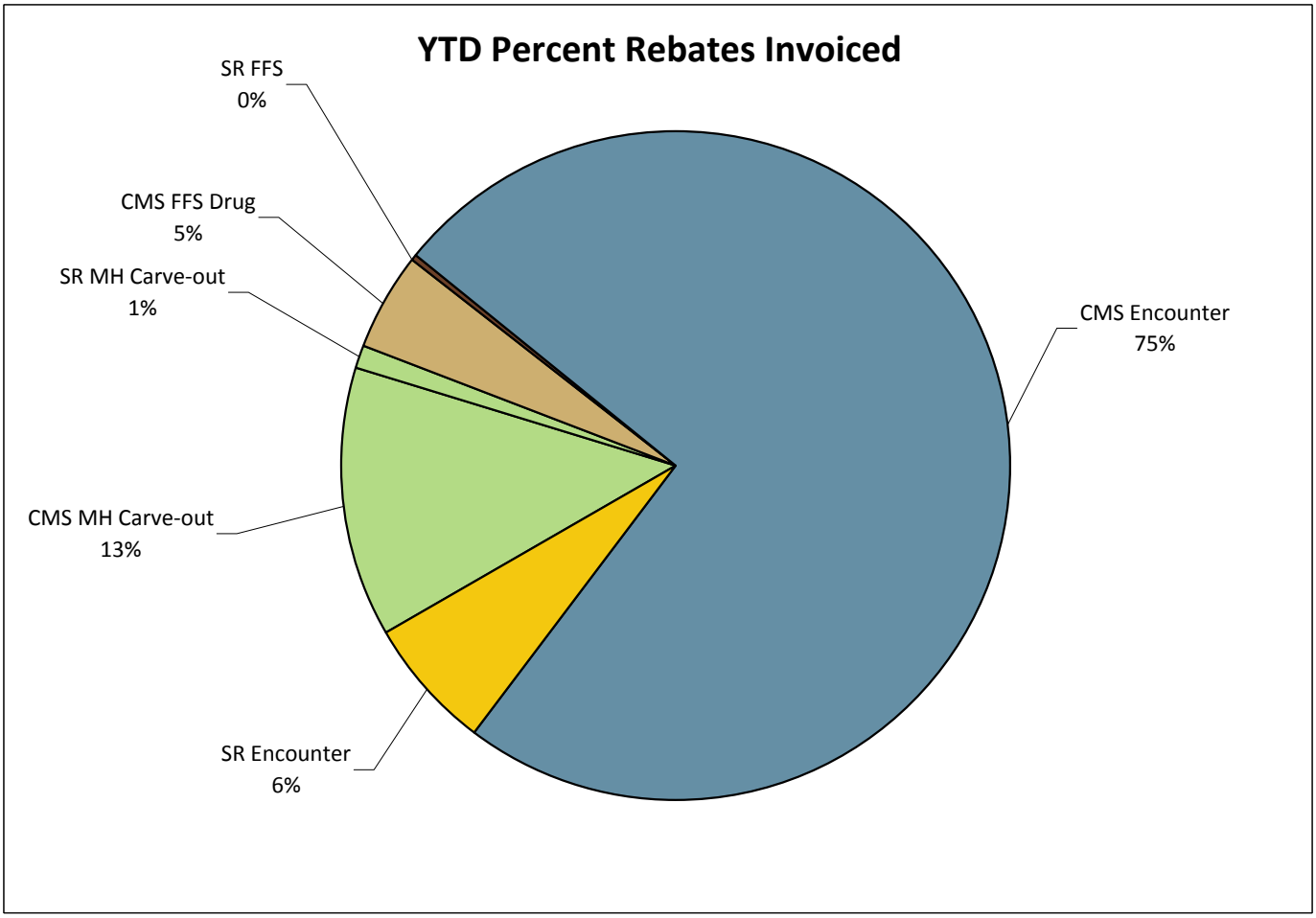
Pharmacy Utilization Summary Report: January 2020 - December 2020

Quarterly Rebates Invoiced	2020-Q1	2020-Q2	2020-Q3	2020-Q4	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$114,343,057	$108,492,684	$116,789,907	$109,670,426	$449,296,074
CMS MH Carve-out	$13,590,035	$12,823,254	$18,665,496	$13,081,395	$58,160,180
SR MH Carve-out	$1,408,756	$1,330,995	$1,335,826	$1,460,965	$5,536,542
CMS FFS Drug	$5,901,275	$5,402,725	$4,693,170	$4,670,025	$20,667,196
SR FFS	$417,105	$473,715	$457,371	$512,651	$1,860,843
CMS Encounter	$86,153,352	$81,409,351	$84,298,151	$82,343,629	$334,204,483
SR Encounter	$6,872,534	$7,052,645	$7,339,892	$7,601,760	$28,866,831

Quaterly Net Drug Costs	2020-Q1	2020-Q2	2020-Q3	2020-Q4	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$154,795,579	$147,569,862	$150,418,347	$163,812,148	$616,595,936
Mental Health Carve-Out Drugs	$12,449,182	$13,113,382	$7,873,777	$14,138,092	$47,574,434
FFS Phys Health + PAD	$7,401,664	$6,032,840	$6,093,132	$6,235,327	$25,762,962
Encounter Phys Health + PAD	$134,944,733	$128,423,640	$136,451,438	$143,438,729	$543,258,540



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

Last Updated: July 22, 2021

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Pharmacy Utilization Summary Report: January 2020 - December 2020

Gross PMPM Drug Costs (Rebates not Subtracted)	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$88.90	$83.56	$97.46	$83.13	$78.74	$84.43	$84.93	$81.59	$81.29	$81.26	$76.52	$85.48	$83.94
Mental Health Carve-Out Drugs	$9.36	$8.65	$9.52	$8.82	$8.44	$8.96	$8.89	$8.51	$8.46	$8.55	$8.14	$8.82	$8.76
FFS Physical Health Drugs	$31.05	$27.98	$30.62	$26.73	$26.78	$28.70	$27.81	$24.37	$25.85	$25.80	$20.77	$23.56	$26.67
FFS Physician Administered Drugs	$15.08	$17.24	$15.79	$10.67	$12.33	$17.59	$17.13	$11.82	$11.48	$16.26	$10.53	$10.55	$13.87
Encounter Physical Health Drugs	$64.87	$61.34	$72.76	$62.92	$58.03	$61.03	$62.59	$60.48	$60.43	$59.65	$57.37	$61.12	$61.88
Encounter Physician Administered Drugs	$18.40	$16.85	$19.80	$15.77	$15.37	$17.14	$16.39	$16.26	$15.83	$16.09	$15.06	$20.08	$16.92

Claim Counts	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Avg Monthly
Total Claim Count (FFS & Encounter)	1,112,318	1,041,516	1,142,821	983,233	990,777	1,048,893	1,057,701	1,038,905	1,055,519	1,088,112	1,031,917	1,088,946	1,056,722
Mental Health Carve-Out Drugs	169,813	157,700	177,010	164,849	164,261	172,263	174,491	171,654	173,437	177,470	174,322	186,810	172,007
FFS Physical Health Drugs	46,519	42,263	45,977	41,247	37,712	39,217	36,786	35,553	36,438	37,792	34,008	36,607	39,177
FFS Physician Administered Drugs	12,900	11,464	10,041	8,916	9,774	10,024	9,985	10,038	9,999	10,343	9,741	10,035	10,272
Encounter Physical Health Drugs	758,153	713,598	805,900	685,358	677,525	715,158	723,359	706,085	722,802	743,124	704,772	743,928	724,980
Encounter Physician Administered Drugs	124,933	116,491	103,893	82,863	101,505	112,231	113,080	115,575	112,843	119,383	109,074	111,566	110,286

Gross Amount Paid per Claim (Rebates not Subtracted)	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$79.47	$79.93	$85.31	$86.77	$82.64	$84.73	$85.53	$84.71	$84.07	$82.54	$83.37	$89.66	$84.06
Mental Health Carve-Out Drugs	$54.80	$54.64	$53.81	$54.90	$53.46	$54.78	$54.27	$53.45	$53.22	$53.28	$52.51	$53.92	$53.92
FFS Physical Health Drugs	$66.48	$65.71	$66.54	$70.66	$66.99	$65.49	$69.57	$66.71	$68.14	$68.10	$67.62	$70.88	$67.74
FFS Physician Administered Drugs	$116.46	$149.25	$157.10	$130.44	$119.05	$156.98	$157.89	$114.64	$110.27	$156.86	$119.70	$115.77	$133.70
Encounter Physical Health Drugs	$76.55	$77.11	$81.29	$84.21	$80.99	$82.20	$84.20	$84.06	$83.24	$80.71	$82.50	$84.80	$81.82
Encounter Physician Administered Drugs	$131.74	$129.76	$171.56	$174.62	$143.17	$147.11	$141.07	$138.07	$139.65	$135.56	$139.97	$185.79	$148.17

Gross Amount Paid per Claim - Generic-Multi Source Drugs (Rebates not Subtracted)	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Avg Monthly
Generic-Multi Source Drugs: Average Paid / Claim (FFS & Encounter)	$19.50	$19.75	$20.09	$19.53	$19.17	$19.47	$20.31	$20.24	$20.58	$20.10	$20.77	$21.35	$20.07
Mental Health Carve-Out Drugs	$17.54	$17.51	$16.67	$16.77	$16.87	$16.94	$16.83	$16.79	$16.33	$16.35	$16.38	$16.55	$16.79
FFS Physical Health Drugs	$21.19	$19.84	$20.17	$20.98	$20.19	$19.93	$20.27	$20.58	$21.21	$21.14	$21.28	$22.62	$20.78
Encounter Physical Health Drugs	$19.88	$20.29	$20.91	$20.19	$19.73	$20.11	$21.24	$21.15	$21.69	$21.06	$21.95	$22.62	$20.90

Gross Amount Paid per Claim - Branded-Single Source Drugs (Rebates not Subtracted)	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Avg Monthly
Branded-Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$489.25	$497.43	$513.95	$548.63	$523.17	$543.40	$556.47	$550.50	$510.38	$477.02	$507.83	$548.72	$522.23
Mental Health Carve-Out Drugs	$1,102.94	$1,095.06	$1,104.65	$1,114.54	$1,103.39	$1,115.05	$1,108.05	$1,104.82	$1,101.14	$1,105.16	$1,084.07	$1,098.85	$1,103.14
FFS Physical Health Drugs	$260.90	$270.87	$265.29	$282.12	$265.54	$261.02	$280.20	$274.94	$271.33	$261.66	$263.97	$281.65	$269.96
Encounter Physical Health Drugs	$472.69	$480.43	$500.09	$535.15	$507.23	$528.52	$540.80	$534.00	$490.86	$455.55	$488.00	$529.78	$505.26

Generic Drug Use Percentage	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Avg Monthly
Generic Drug Use Percentage	88.8%	88.9%	88.7%	88.9%	88.9%	89.1%	89.2%	89.2%	88.5%	88.0%	88.6%	89.2%	88.8%
Mental Health Carve-Out Drugs	96.6%	96.6%	96.6%	96.5%	96.6%	96.6%	96.6%	96.6%	96.6%	96.6%	96.6%	96.5%	96.6%
FFS Physical Health Drugs	81.1%	81.7%	81.1%	81.0%	80.9%	81.1%	81.0%	81.9%	81.2%	80.5%	80.9%	81.4%	81.2%
Encounter Physical Health Drugs	87.5%	87.7%	87.4%	87.6%	87.4%	87.8%	87.9%	87.7%	86.9%	86.3%	87.0%	87.7%	87.4%

Preferred Drug Use Percentage	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Oct-20	Nov-20	Dec-20	Avg Monthly
Preferred Drug Use Percentage	85.16%	85.07%	85.16%	84.90%	84.79%	85.05%	85.40%	85.31%	86.80%	86.71%	86.70%	86.68%	85.6%
Mental Health Carve-Out Drugs	73.13%	73.07%	73.28%	73.16%	72.87%	73.05%	72.83%	72.84%	77.40%	77.28%	77.16%	77.37%	74.5%
FFS Physical Health Drugs	94.68%	94.29%	93.74%	89.25%	89.21%	89.00%	94.26%	94.24%	94.70%	94.37%	94.28%	94.80%	93.1%
Encounter Physical Health Drugs	87.29%	87.20%	87.27%	87.41%	87.39%	87.67%	87.95%	87.88%	88.66%	88.60%	88.71%	88.62%	87.9%

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 22, 2021

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

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	LATUDA	Antipsychotics, 2nd Gen	$6,973,871	15.8%	5,731	$1,217	Y
2	INVEGA SUSTENNA	Antipsychotics, Parenteral	$3,455,051	7.8%	1,600	$2,159	Y
3	VRAYLAR	Antipsychotics, 2nd Gen	$2,545,534	5.8%	2,230	$1,141	Y
4	STRATTERA*	ADHD Drugs	$2,433,066	5.5%	5,221	$466	Y
5	INVEGA	Antipsychotics, 2nd Gen	$2,373,206	5.4%	1,835	$1,293	V
6	REXULTI	Antipsychotics, 2nd Gen	$1,927,868	4.4%	1,693	$1,139	V
7	ABILIFY MAINTENA	Antipsychotics, Parenteral	$1,825,037	4.1%	855	$2,135	Y
8	INVEGA TRINZA	Antipsychotics, Parenteral	$884,160	2.0%	134	$6,598	Y
9	ARISTADA	Antipsychotics, Parenteral	$753,394	1.7%	322	$2,340	Y
10	TRINTELLIX	Antidepressants	$710,240	1.6%	1,715	$414	V
11	SERTRALINE HCL	Antidepressants	$588,570	1.3%	56,721	$10	Y
12	BUPROPION XL	Antidepressants	$532,286	1.2%	36,221	$15	Y
13	DULOXETINE HCL	Antidepressants	$529,509	1.2%	35,406	$15	Y
14	VIIBRYD	Antidepressants	$528,041	1.2%	1,733	$305	V
15	FLUOXETINE HCL	Antidepressants	$483,099	1.1%	40,808	$12	Y
16	TRAZODONE HCL	Antidepressants	$447,339	1.0%	45,051	$10	
17	ESCITALOPRAM OXALATE	Antidepressants	$364,148	0.8%	36,485	$10	Y
18	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	$311,882	0.7%	24,091	$13	
19	LAMOTRIGINE	Antiepileptics (non-injectable)	$299,087	0.7%	27,742	$11	Y
20	RISPERDAL CONSTA*	Antipsychotics, Parenteral	$298,726	0.7%	333	$897	Y
21	PFIZER COVID-19 VACCINE (EUA)	STC 90 - Biologicals	$294,669	0.7%	7,382	$40	
22	BIKTARVY	HIV	$273,766	0.6%	96	$2,852	Y
23	CHOLBAM*	Bile Therapy	$248,984	0.6%	6	$41,497	N
24	LAMOTRIGINE ER	Antiepileptics (non-injectable)	$243,034	0.6%	2,749	$88	V
25	ARIPIPRAZOLE	Antipsychotics, 2nd Gen	$234,396	0.5%	18,272	$13	Y
26	VENLAFAXINE HCL ER	Antidepressants	$213,998	0.5%	18,090	$12	Y
27	QUETIAPINE FUMARATE*	Antipsychotics, 2nd Gen	$213,715	0.5%	18,976	$11	Y
28	AMITRIPTYLINE HCL*	Antidepressants	$209,722	0.5%	14,648	$14	Y
29	BUPROPION XL	Antidepressants	$200,933	0.5%	931	$216	V
30	Inj, Nusinersen, 0.1mg	Physican Administered Drug	$199,020	0.5%	1	$199,020	
31	VENLAFAXINE HCL ER	Antidepressants	$198,027	0.4%	2,212	$90	V
32	CITALOPRAM HBR	Antidepressants	$190,110	0.4%	21,710	$9	Y
33	SPRAVATO*	Antidepressants	$178,357	0.4%	162	$1,101	V
34	CONCERTA*	ADHD Drugs	$170,873	0.4%	525	$325	N
35	Epoetin Alfa, 100 Units Esrd	Physican Administered Drug	$159,059	0.4%	569	$280	
36	WELLBUTRIN XL	Antidepressants	$156,203	0.4%	195	$801	Y
37	MIRTAZAPINE	Antidepressants	$155,924	0.4%	10,593	$15	Y
38	Inj Pembrolizumab	Physican Administered Drug	$155,809	0.4%	36	$4,328	
39	LANTUS SOLOSTAR*	Diabetes, Insulins	$153,845	0.3%	436	$353	Y
40	OLANZAPINE	Antipsychotics, 2nd Gen	$153,774	0.3%	11,987	$13	Y
		Top 40 Aggregate:	**$32,268,333**		**455,503**	**$6,782**	
		All FFS Drugs Totals:	**$44,127,766**		**692,877**	**$583**	

*** Drug requires Prior Authorization**

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

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

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	PFIZER COVID-19 VACCINE (EUA)	STC 90 - Biologicals	$294,669	3.0%	7,382	$40	
2	BIKTARVY	HIV	$273,766	2.8%	96	$2,852	Y
3	CHOLBAM*	Bile Therapy	$248,984	2.6%	6	$41,497	N
4	Inj, Nusinersen, 0.1mg	Physican Administered Drug	$199,020	2.0%	1	$199,020	
5	CONCERTA*	ADHD Drugs	$170,873	1.8%	525	$325	N
6	Epoetin Alfa, 100 Units Esrd	Physican Administered Drug	$159,059	1.6%	569	$280	
7	Inj Pembrolizumab	Physican Administered Drug	$155,809	1.6%	36	$4,328	
8	LANTUS SOLOSTAR*	Diabetes, Insulins	$153,845	1.6%	436	$353	Y
9	MODERNA COVID-19 VACCINE (EUA	STC 90 - Biologicals	$131,522	1.4%	3,318	$40	
10	Inj., Emicizumab-Kxwh 0.5 Mg	Physican Administered Drug	$129,086	1.3%	6	$21,514	
11	HUMIRA(CF) PEN*	Biologics for Autoimmune Conditions	$128,762	1.3%	40	$3,219	Y
12	SABRIL	Antiepileptics (non-injectable)	$126,172	1.3%	3	$42,057	N
13	ELIQUIS	Anticoagulants, Oral and SQ	$115,142	1.2%	313	$368	Y
14	VYVANSE*	ADHD Drugs	$111,945	1.2%	661	$169	Y
15	TRULICITY*	Diabetes, GLP-1 Receptor Agonists	$110,418	1.1%	211	$523	Y
16	IBRANCE*	Antineoplastics, Newer	$105,428	1.1%	9	$11,714	
17	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$103,842	1.1%	11	$9,440	Y
18	ENBREL SURECLICK*	Biologics for Autoimmune Conditions	$101,547	1.0%	25	$4,062	Y
19	Etonogestrel Implant System	Physican Administered Drug	$99,582	1.0%	143	$696	
20	VIMPAT	Antiepileptics (non-injectable)	$99,411	1.0%	230	$432	Y
21	BUPRENORPHINE-NALOXONE*	Substance Use Disorders, Opioid & Alcohol	$93,872	1.0%	1,408	$67	Y
22	Aflibercept Injection	Physican Administered Drug	$91,166	0.9%	182	$501	
23	ALBUTEROL SULFATE HFA	Beta-Agonists, Inhaled Short-Acting	$88,716	0.9%	2,463	$36	Y
24	Injection, Ocrelizumab, 1 Mg	Physican Administered Drug	$85,435	0.9%	10	$8,543	
25	OPSUMIT*	Pulmonary Arterial Hypertension Oral and Inhale	$84,652	0.9%	8	$10,582	N
26	Inj. Pemetrexed Nos 10mg	Physican Administered Drug	$79,142	0.8%	38	$2,083	
27	ISTURISA*	STC 64 - Other Hormones	$75,620	0.8%	2	$37,810	
28	TRIKAFTA*	Cystic Fibrosis	$72,419	0.7%	14	$5,173	N
29	FLOVENT HFA	Corticosteroids, Inhaled	$70,076	0.7%	439	$160	Y
30	LANTUS	Diabetes, Insulins	$67,656	0.7%	165	$410	Y
31	Inj, Ado-Trastuzumab Emt 1mg	Physican Administered Drug	$67,628	0.7%	11	$6,148	
32	Mirena, 52 Mg	Physican Administered Drug	$65,070	0.7%	99	$657	
33	COSENTYX PEN (2 PENS)*	Biologics for Autoimmune Conditions	$63,613	0.7%	16	$3,976	N
34	AFINITOR DISPERZ*	Antineoplastics, Newer	$63,009	0.6%	11	$5,728	
35	Factor Viii Recomb Novoeight	Physican Administered Drug	$60,688	0.6%	2	$30,344	
36	ADVATE	Antihemophilia Factors	$59,456	0.6%	4	$14,864	
37	Infliximab Not Biosimil 10mg	Physican Administered Drug	$56,149	0.6%	50	$1,123	
38	CHANTIX*	Tobacco Smoking Cessation	$55,587	0.6%	137	$406	Y
39	ETONOGESTREL-ETHINYL ESTRADIOI	STC 63 - Oral Contraceptives	$55,519	0.6%	281	$198	
40	PULMOZYME	Cystic Fibrosis	$55,487	0.6%	35	$1,585	Y
		Top 40 Aggregate:	**$4,429,841**		**19,396**	**$11,833**	
		All FFS Drugs Totals:	**$9,711,585**		**128,437**	**$598**	

*** Drug requires Prior Authorization**

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

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Prior Authorization Criteria Update: Oncology

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

Table 1. New oncology drugs

Generic Name	Brand Name
Amivantamab-vmjw	RYBREVANT
Infigratinib	TRUSELTIQ
Sotorasib	LUMAKRAS

Recommendation:

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

Oncology Agents

Goal(s):

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

Length of Authorization:

- Up to 1 year

Requires PA:

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

Covered Alternatives:

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

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

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

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

Table 1. Oncology agents which apply to this policy (Updated 07~~5~~/02~~3~~/2021)
New Antineoplastics are immediately subject to the policy and will be added to this table at the next P&T Meeting

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

Generic Name	Brand Name
capmatinib	TABRECTA
carfilzomib	KYPROLIS
cemiplimab-rwlc	LIBTAYO
ceritinib	ZYKADIA
cobimetinib fumarate	COTELLIC
copanlisib di-HCl	ALIQOPA
crizotinib	XALKORI
dabrafenib mesylate	TAFINLAR
dacomitinib	VIZIMPRO
daratumumab	DARZALEX
daratumumab/hyaluronidase-fihj	DARZALEX FASPRO
darolutamide	NUBEQA
decitabine and cedazuridine	INQOVI
degarelix acetate	FIRMAGON
dostarlimab-gxly	JEMPERLI
dinutuximab	UNITUXIN
durvalumab	IMFINZI
duvelisib	COPIKTRA
elotuzumab	EMPLICITI
enasidenib mesylate	IDHIFA
encorafenib	BRAFTOVI
enfortumab vedotin-ejfv	PADCEV
entrectinib	ROZLYTREK
enzalutamide	XTANDI
erdafitinib	BALVERSA
eribulin mesylate	HALAVEN
everolimus	AFINITOR
everolimus	AFINITOR DISPERZ
fam-trastuzumab deruxtecan-nxki	ENHERTU
fedratinib	INREBIC
gilteritinib	XOSPATA
glasdegib	DAURISMO

Generic Name	Brand Name
ibrutinib	IMBRUVICA
idecabtagene vicleucel	ABECMA
idelalisib	ZYDELIG
infigratinib	TRUSELTIQ
ingenol mebutate	PICATO
inotuzumab ozogamicin	BESPONSA
ipilimumab	YERVOY
Isatuximab	SARCLISA
ivosidenib	TIBSOVO
ixazomib citrate	NINLARO
larotrectinib	VITRAKVI
lenvatinib mesylate	LENVIMA
lisocabtagene maraleucel	BREYANZI
loncastuximab tesirine-lpyl	ZYNLONTA
lorlatinib	LORBRENA
lurbinectedin	ZEPZELCA
lutetium Lu 177 dotate	LUTATHERA
margetuximab-cmkb	MARGENZA
melphalan flufenamide	PEPAXTO
midostaurin	RYDAPT
moxetumomab pasudotox-tdfk	LUMOXITI
naxitamab-gqgk	DANYELZA
necitumumab	PORTRAZZA
neratinib maleate	NERLYNX
niraparib tosylate	ZEJULA
nivolumab	OPDIVO
obinutuzumab	GAZYVA
ofatumumab	ARZERRA
olaparib	LYNPARZA
olaratumab	LARTRUVO
olatuzumab vedotin-piiq	POLIVY
omacetaxine mepesuccinate	SYNRIBO
osimertinib mesylate	TAGRISSO

Generic Name	Brand Name
palbociclib	IBRANCE
panobinostat lactate	FARYDAK
pazopanib HCl	VOTRIENT
pembrolizumab	KEYTRUDA
pemigatinib	PEMAZYRE
pertuzumab	PERJETA
pertuzumab/trastuzumab/haluronidase-zzxf	PHESGO
pexidartinib	TURALIO
polatuzumab vedotin-piiq	POLIVY
pomalidomide	POMALYST
ponatinib	ICLUSIG
pralatrexate	FOLOTYN
pralsetinib	GAVRETO
ramucirumab	CYRAMZA
regorafenib	STIVARGA
relugolix	ORGOVYZ
ribociclib succinate	KISQALI
ribociclib succinate/letrozole	KISQALI FEMARA CO-PACK
ripretinib	QINLOCK
romidepsin	ISTODAX
romidepsin	ROMIDEPSIN
rucaparib camsylate	RUBRACA
ruxolitinib phosphate	JAKAFI
sacitizumab govitecan-hziy	TRODELVY
selinexor	XPOVIO
selpercatinib	RETEVMO
siltuximab	SYLVANT
sipuleucel-T/lactated ringers	PROVENGE
sonidegib phosphate	ODOMZO
sotorasib	LUMAKRAS
tafasitamab-cxix	MONJUVI
tagraxofusp-erzs	ELZONRIS

Generic Name	Brand Name
talazoparib	TALZENNA
talimogene laherparepvec	IMLYGIC
tazemetostat	TAZVERIK
tepotinib	TEPMETKO
tisagenlecleucel	KYMRIAH
tivozanib	FOTIVDA
trabectedin	YONDELIS
trametinib dimethyl sulfoxide	MEKINIST
trastuzumab-anns	KANJINTI
trastuzumab-dkst	OGIVRI
trastuzumab-dttb	ONTRUZANT
trastuzumab-hyaluronidase-oysk	HERCEPTIN HYLECTA
trastuzumab-pkrb	HERZUMA
trastuzumab-qyyp	TRAZIMERA
trifluridine/tipiracil HCl	LONSURF
trilaciclib	COSELA
tucatinib	TUKYSA
umbralisib	UKONIQ
vandetanib	VANDETANIB
vandetanib	CAPRELSA
vemurafenib	ZELBORAF
venetoclax	VENCLEXTA
venetoclax	VENCLEXTA STARTING PACK
vismodegib	ERIVEDGE
zanubrutinib	BRUKINSA
ziv-aflibercept	ZALTRAP

ProDUR Report for April through June 2021
High Level Summary by DUR Alert

DUR Alert	Example	Disposition	# Alerts	# Overrides	# Cancellations	# Non-Response	% of all DUR Alerts	% Overridden
DA (Drug/Allergy Interaction)	Amoxicillin billed and Penicillin allergy on patient profile	Set alert/Pay claim	4	2	0	2	0.01%	**N/A**
DC (Drug/Inferred Disease Interaction)	Quetiapine billed and condition on file for Congenital Long QT Sundrome	Set alert/Pay claim	2,311	474	0	1,837	1.73%	**N/A**
DD (Drug/Drug Interaction)	Linezolid being billed and patient is on an SNRI	Set alert/Pay claim	6,797	1,678	0	5,117	5.17%	**N/A**
ER (Early Refill)	Previously filled 30 day supply and trying to refill after 20 days (80% = 24 days)	Set alert/Deny claim	85,856	15,209	32	70,607	65.87%	**17.7%**
ID (Ingredient Duplication)	Oxycodone IR 15mg billed and patient had Oxycodone 40mg ER filled in past month	Set alert/Pay claim	24,907	6,032	8	18,862	19.07%	**N/A**
LD (Low Dose)	Divalproex 500mg ER billed for 250mg daily (#15 tabs for 30 day supply)	Set alert/Pay claim	760	148	0	612	0.57%	**N/A**
LR (Late Refill/Underutilization)	Previously filled for 30 days supply and refill being billed 40 days later.	Set alert/Pay claim	3	3	0	0	0.01%	**N/A**
MC (Drug/Disease Interaction)	Bupropion being billed and patient has a seizure disorder	Set alert/Pay claim	926	257	0	669	0.70%	**N/A**
MX (Maximum Duration of Therapy)		Set alert/Pay claim	424	133	0	291	0.27%	**N/A**
PG (Pregnancy/Drug Interaction)	Accutane billed and client has recent diagnosis history of pregnancy	Set alert/Deny claim	17	10	0	7	0.02%	**58.8%**
TD (Therapeutic Duplication)	Diazepam being billed and patient recently filled an Alprazolam claim.	Set alert/Pay claim	8,332	2,075	0	6,256	6.33%	**N/A**
		Totals	**130,337**	**26,021**	**40**	**104,260**	**99.74%**	**20.0%**

ProDUR Report for April through June 2021

Top Drugs in Enforced DUR Alerts

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Remeron (Mirtazapine)	1,714	270	1,444	14,157	12.1%	15.8%
ER	Lorazepam	298	89	209	13,033	2.3%	29.9%
ER	Alprazolam	169	40	129	7,741	2.2%	23.7%
ER	Diazepam	120	36	84	4,674	2.6%	30.0%
ER	Buspirone (Buspar)	3,122	463	2,656	32,400	9.6%	14.8%
ER	Lamictal (Lamotrigine)	5,504	1,004	4,500	42,903	12.8%	18.2%
ER	Seroquel (Quetiapine)	4,074	832	3,242	30,468	13.4%	20.4%
ER	Zyprexa (Olanzapine)	2,444	507	1,937	19,015	12.9%	20.7%
ER	Risperdal (Risperidone)	1,752	367	1,385	13,608	12.9%	20.9%
ER	Abilify (Aripiprazole)	3,379	502	2,877	27,110	12.5%	14.9%
ER	Wellbutrin (Bupropion)	5,930	834	5,096	66,889	8.9%	14.1%
ER	Suboxone (Buprenorphine/Naloxone)	94	36	58	2,047	4.6%	38.3%
ER	Zoloft (Sertraline)	7,552	1,304	6,248	74,474	10.1%	17.3%
ER	Prozac (Fluoxetine)	5,153	768	4,385	53,716	9.6%	14.9%
ER	Lexapro (Escitalopram)	4,594	694	3,900	47,782	9.6%	15.1%
ER	Celexa (Citalopram)	2,228	325	1,903	27,132	8.2%	14.6%
ER	Trazodone	5,935	1,003	4,932	57,694	10.3%	16.9%
ER	Cymbalta (Duloxetine)	4,360	704	3,656	44,982	9.7%	16.1%
ER	Intuniv (Guanfacine)	1,764	213	1,551	13,086	13.5%	12.1%

ProDUR Report for April through June 2021
Early Refill Reason Codes

DUR Alert	Month	# Overrides	CC-3 Vacation Supply	CC-4 Lost Rx	CC-5 Therapy Change	CC-6 Starter Dose	CC-7 Medically Necessary	CC-13 Emergency Disaster	CC-14 LTC Leave of Absence	CC-Other
ER	April	3,365	122	237	721	2	1,997	139	0	147
ER	May	4,025	152	305	887	9	2,400	139	0	133
ER	June	3,603	200	252	809	2	2,094	127	0	119
	Total =	**10,993**	**474**	**794**	**2,417**	**13**	**6,491**	**405**	**0**	**399**
	Percentage of total overrides =		**4.3%**	**7.2%**	**22.0%**	**0.1%**	**59.0%**	**3.7%**	**0.0%**	**3.6%**

ProDUR Report for April through June 2021

DUR Alert Cost Savings Report

Month	Alert Type	Prescriptions Not Dispensed	Cost Savings
Apr-21	DD	1	$199.99
Apr-21	ER	60	$12,501.83
Apr-21	HD	1	$101.11
Apr-21	ID	3	$877.17
Apr-21	TD	2	$222.07
		April Savings =	**$13,902.17**
May-21	DD	1	$2,094.13
May-21	ER	16	$14,755.42
May-21	ID	7	$1,622.34
		May Savings =	**$18,471.89**
Jun-21	DD	4	$151.94
Jun-21	ER	31	$5,520.08
Jun-21	ID	10	$1,404.53
	TD	4	$1,616.95
		June Savings =	**$8,693.50**
		Total 2Q2021 Savings =	**$41,067.56**

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Retro-DUR Intervention History by Quarter FFY 2020 - 2021

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Change Form	Desvenlafaxine Salt Formulations	Unique Prescribers Identified		52	48	
		Unique Patients Identified		53	48	
		Total Faxes Successfully Sent		44	27	
		Prescriptions Changed to Recommended Within 6 Months of Intervention		24	17	
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention		$19,209	$5,895	
	Fluoxetine Tabs to Caps	Unique Prescribers Identified	23			
		Unique Patients Identified	23			
		Total Faxes Successfully Sent	15			
		Prescriptions Changed to Recommended Within 6 Months of Intervention	7			
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$654			
	Venlafaxine Tabs to Caps	Unique Prescribers Identified	146	293	210	14
		Unique Patients Identified	147	300	215	14
		Total Faxes Successfully Sent	99	210	101	1
		Prescriptions Changed to Recommended Within 6 Months of Intervention	84	127	65	1
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$80,550	$71,983	$22,030	$54

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Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Cost Savings	RetroDUR Dose Consolidation	Total Claims Identified	51	50	77	31
		Total Faxes Successfully Sent	10	17	11	
		Prescriptions Changed to Recommended Dose Within 3 Months of Fax Sent	4	9	3	
		Prescriptions Changed to Alternative Dose Within 3 Months of Fax Sent	11	2		
		Prescriptions Unchanged after 3 Months of Fax Sent	28	29	20	
		Safety Monitoring Profiles Identified	7	10	2	
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Faxes Sent	($7,718)	$14,231	$3,875	

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Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Expert Consultation Referral	Long Term Antipsychotic Use in Children	Total patients identified with >90 days of antipsychotic use	936	606	878	272
		High risk patients identified	13	6	7	
		Prescribers successfully notified	13	6	7	
		Patients with change in antipsychotic drug in following 90 days	2			
		Patients with continued antipsychotic therapy in the following 90 days	8	6	7	
		Patients with discontinuation of antipsychotic therapy in the following 90 days	2			

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Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Non-Adherence	Antipsychotics in people w/schizophrenia	Total patients identified	69	66	52	20
		Total prescribers identified	68	66	52	20
		Prescribers successfully notified	68	66	46	17
		Patients with claims for the same antipsychotic within the next 90 days	37	36	25	5
		Patients with claims for a different antipsychotic within the next 90 days	5	4	3	

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Retro-DUR Intervention History by Quarter FFY 2020 - 2021

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Profile Review	Foster care children under age 12 on antipsychotic	RetroDUR_Profiles Reviewed	75	159	59	27
	Foster care children under age 18 on 3 or more psychotropics	RetroDUR_Profiles Reviewed	18	27	12	20
	Foster care children under age 18 on any psychotropic	RetroDUR_Profiles Reviewed	113	237	134	60
	Foster care children under age 6 on any psychotropic	RetroDUR_Profiles Reviewed	17	31	21	13
	High Risk Patients - Bipolar	RetroDUR_Profiles Reviewed				2
	High Risk Patients - Opioids	RetroDUR_Profiles Reviewed	10		10	
		RetroDUR_Letters Sent To Providers	4		4	
	High Risk Patients - Polypharmacy	RetroDUR_Profiles Reviewed			1	
		RetroDUR_Letters Sent To Providers			2	
	Lock-In	RetroDUR_Profiles Reviewed	14	20	25	
		RetroDUR_Letters Sent To Providers	2	1	1	
		Locked In	1	1	1	
	Polypharmacy	RetroDUR_Profiles Reviewed	27	16	26	12
		RetroDUR_Letters Sent To Providers	6	3	4	

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Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Safety Net: PA Denials with no subsequent PA requested or dangerous drug combinations	Combination Opioid-Sedative	Total patients identified	120	123	122	34
		Total prescribers identified	119	123	121	34
		Prescribers successfully notified	112	110	99	19
		Patients with discontinuation of therapy within next 90 days	29	25	25	25
		Patients with new prescription for naloxone within next 90 days	4	4	2	
		Average number of sedative drugs dispensed within next 90 days	24	24	20	1
		Average number of sedative prescribers writing prescriptions in next 90 days	24	24	20	1
	Denied Claims due to Antipsychotic Dose Consolidation	Total patients identified		62	75	15
		Patients with a paid claim for the drug (based on HSN) within 14 days		37	50	8
		Patients without a paid claim within 14 days		25	25	
	ICS/LABA	ICS/LABA Denials	26	21	36	8
		Disqualified	6	6	11	3
		Disqualified - Erroneous denial	6	6	11	3
		Faxes Sent	1	2		
		Fax Sent - Combination Inhaler	1	1		
		No Subsequent Pulmonary Claims		1		
	Oncology Denials	Total patients identified	1	3		1
		Total prescribers identified	1	3		1
		Prescribers successfully notified	1	1		
		Patients with claims for the same drug within the next 90 days	1	2		
		Patients with claims for any oncology agent within the next 90 days	1	2		1

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

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Antidepressant Review

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Depression is the second leading cause of disability in the United States (US), following cardiovascular disease, and the leading cause of disability worldwide.[1] There have been many recent challenges which has resulted in rising incidences of depression. Examples of these include Coronavirus Disease-2019 (COVID-19), loss of employer-provided health insurance, the opioid pandemic, job termination and isolation. The Centers for Disease Control and Prevention (CDC) has reported increases in mental health challenges, with 40% of adults in the US reporting issues with mental health or substance abuse.[2] Depressive disorders were approximately four times higher in April-June of 2020 compared to the same time period in 2019.[2] Populations that have seen the largest increase in depressive disorders are younger adults, racial/ethnic minorities, essential workers and unpaid adult caregivers. The most recent report from the CDC on state specific rates found Oregon to be ranked the highest in the country in depression rates.[3] In Medicaid patients served by the Oregon Health Plan (OHP) there were over 133,000 patients with antidepressant claims in the second quarter of 2020.[4] Persons with mental health disorders are at least 10 times as likely to commit suicide or have a suicide attempt, emphasizing the importance of appropriate managment.[5] The combination of non-pharmacologic strategies, like behavioral counseling, with antidepressants can be important tools in optimizing patient care. This newsletter will focus on initiating, tapering, and switching antidepressants with a brief update on the use of esketamine.

Antidepressants

Providers are familiar with the classes of antidepressants that are available, which include: selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), atypical agents (bupropion and mirtazapine), serotonin modulators, tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs). Classes of antidepressants are differentiated by their mechanisms of action, which corresponds to differing adverse event profiles. Food and Drug Administration (FDA) indications for antidepressants include depression, anxiety disorders and pain conditions. The National Institute for Health and Care Excellence (NICE) and American Psychiatric Association (APA) recommend second-generation antidepressants (SSRIs, SNRIs, or atypical agents) for initial treatment.[6,7] There is a lack of evidence from high quality systematic reviews that one second-generation antidepressant is superior to another; therefore, treatment selection should be based on adverse events, patient specific characteristics, tolerability and cost.

Antidepressant Adverse Events

Minimizing adverse events can increase adherence and treatment success of antidepressant therapy. Common antidepressant adverse reactions are sexual dysfunction, anticholinergic effects, drowsiness, insomnia/agitation, orthostatic hypotension, QTc prolongation, gastrointestinal adverse reactions and weight gain.[8] Antidepressants with a moderate to high risk of certain adverse reactions are presented in **Table 1.** Antidepressants in **Table 2** are associated with less risk of common adverse reactions to help providers select the most appropriate therapy. Boxed warnings are part of the prescribing information for all antidepressants due to the risk of suicidal thoughts and behaviors in pediatric and young adult populations and therefore, these populations should be monitored more closely.

Table 1. Antidepressants Associated with Moderate to High Levels of Certain Adverse Reactions*[8,9]

Antidepressant	Adverse Reaction	Level of Risk
Citalopram	QTc Prolongation	Moderate
Citalopram	Sexual Dysfunction	High
Escitalopram **Fluoxetine** **Paroxetine** **Sertraline**	Sexual Dysfunction	Moderate
Mirtazapine	Drowsiness	High
Mirtazapine	Weight gain	High
Venlafaxine	Sexual Dysfunction	Moderate
Trazodone	Drowsiness	High
Trazodone	Orthostatic Hypotension	Moderate
Trazodone	GI adverse reactions	Moderate
Vilazodone	GI adverse reactions	High
Vortioxetine	GI adverse reactions	Moderate

Key: * Other antidepressants may be associated with these adverse reactions but at slight or low risk.

Table 2. Antidepressant Recommendations for Minimization of Certain Adverse Reactions[8]

Adverse Reaction to be Avoided	Antidepressants with the Least Risk
Sexual Dysfunction	• Bupropion • Mirtazapine • Duloxetine • Vortioxetine • Nefazodone
Drowsiness	• SSRIs • SNRIs • Bupropion • Vilazodone • Vortioxetine
Anticholinergic	• SSRIs^ • SNRIs • Serotonin modulators* • Bupropion
Orthostatic hypotension	• Atypical agents† • SNRIs
QTc Prolongation	• SNRIs • Atypical agents† • Nefazodone • Vilazodone • vortioxetine
Weight gain	• Bupropion • Fluoxetine • SNRIs • Serotonin modulators*

Abbreviations: SNRIs – serotonin-norepinephrine reuptake inhibitors; SSRIs – selective serotonin reuptake inhibitors
Key: * Nefazodone, trazodone, vilazodone, vortioxetine; † Bupropion, mirtazapine; ^ Paroxetine is not recommended if anticholinergic adverse reactions are to be avoided

Switching Antidepressants

Antidepressant therapy should be tried for a minimum of 4 weeks after dose optimization to determine success of therapy. Remission of depressive symptoms with the use of an initial antidepressant treatment only occurs in around one-third of patients, thus necessitating switching to a different antidepressant.[10] There is limited evidence to guide changing antidepressants but in general, if two therapies from the same class have not been effective, it is recommended to try an option from a different class. Suggested guidance for switching antidepressants depends on the class, half-life and specific drug characteristics (**Table 3**). Caution is warranted due to lack of data on switching the following therapies: vortioxetine, vilazodone, desvenlafaxine, or levomilnacipran.[10]

Table 3. Key Strategies for Switching Antidepressants[10]

Strategies	Explanation	Recommended Classes	Examples
Abrupt switch	Stop the initial therapy and start the new one at a low dose	- SSRI to SSRI+ - SSRI to SNRI - SNRI to SSRI - SNRI to mirtazapine+	Citalopram to sertraline 25 mg/day
Cross-tapering*	Gradually increase the dose of the new therapy while decreasing the existing therapy	- SSRI to SSRI+ - SSRI to mirtazapine - mirtazapine to SSRI - SNRI to mirtazapine+ - Switching to or from bupropion	Sertraline 50 mg daily to mirtazapine 15 mg daily
Taper and switch	Taper high dose antidepressant to a low dose before starting new therapy	- High dose SSRI to new SSRI	Taper paroxetine by 25% every 4 to 6 weeks to 10 mg daily and then start sertraline 25 mg daily
Taper and switch with washout	Gradually taper dose, stop current medication and allow for washout	- Fluoxetine (4-7 day washout) to venlafaxine or duloxetine	Taper and stop fluoxetine. After washout start venlafaxine 37.5 mg/day

Abbreviations: SNRIs – serotonin-norepinephrine reuptake inhibitors; SSRIs – selective serotonin reuptake inhibitors
Key: * Not recommended with fluoxetine, which should be stopped and the new SSRI should be started after a 7-day washout; + Abrupt switch or cross-tapering can be used

When switching or discontinuing antidepressants there is a risk of discontinuation syndrome. Tapering antidepressants over 6-8 weeks is recommended to avoid this syndrome; however, it can still occur. Discontinuation syndrome can last up to 2 weeks and is due to the effects of decreasing levels of serotonin and down regulation of receptors. Discontinuation syndrome presents as gastrointestinal flu-like symptoms, irritability, insomnia, dizziness, vivid dreams and paresthesias.[11] The syndrome is most often seen when switching from a serotonergic antidepressant to a nonserotonergic treatment (e.g., switching from venlafaxine or paroxetine to buproprion) and with therapies with a shorter half-life.[10] Discontinuation syndromes can be treated by increasing the dose of the serotonergic agent, repeating the taper at a slower rate or switching the patient to an SSRI with a longer half-life.[11]

Esketamine

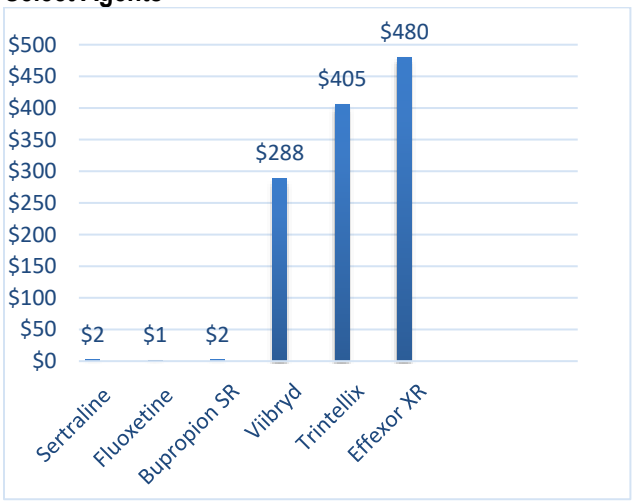
Esketamine is a non-competitive N-methyl-D-aspartate (NMDA) receptor blocker initially approved for treatment-resistant depression.[12] Esketamine must be given under the supervision of a provider and is only available through a Risk Evaluation and Mitigation Strategy (REMs) Program. It is indicated for use along with an oral antidepressant. Esketamine is associated with nausea, vomiting, dissociation, sedation, and misuse. Blood pressure should also be monitored as elevations have been seen for up to 4 hours. Esketamine, 56 or 84 mg, is given as a nasal spray twice weekly for the first month and then once weekly or every other week as maintenance therapy.[12] The cost for esketamine for a 30-day supply (given once weekly) is $1585.[13]

Esketamine received an expanded indication for major depressive disorder with suicidality in July of 2020.[12] Two, four-week randomized clinical trials demonstrated mean improvements in the Montgomery-Asberg Depression Rating Scale (MADRS) scale of 15.7-16.4 points with esketamine compared to 12.4-12.8 points for those treated with placebo, measured from baseline to 24 hours.[14,15] Patients with higher MADRS scores or those with prior suicide attempt demonstrated more improvement in depressive symptoms with esketamine use. The decrease in acute suicidality (median of 1 point on the Clinical Global Impression–Severity of Suicidality–revised [CGI-SS-r] scale) was the same in the esketamine group and placebo group.[14,15] Providers should be aware that although the new indication for esketamine would suggest an improvement in suicidal ideation, this was ***not*** demonstrated in the trials.

Comparative Antidepressant Costs

There are many antidepressant options available to choose from, with generic products representing the best value. A small selection of antidepressant comparative costs, based on average actual acquisition cost (AAAC), illustrate the dramatic differences in a 30-day supply (**Figure 1)**.

Figure 1. Comparative Antidepressant Monthly Cost for Select Agents



* Prices based on Myers and Stauffer Average Actual Acquisition Cost (AAAC) January 26, 2021. Available at: https://www.mslc.com/uploadedFiles/Oregon/AACArchive/OHA%20Generic%20Web%20Listing_20210126_State.pdf

Conclusion

In a time when many people are encountering depressive symptoms, optimizing antidepressant therapy is increasingly important. Choosing treatment options to minimize adverse reactions according to patient preferences and comorbidities will position patients to successfully adhere to therapy. Switching between antidepressants is common and can be done in a way to minimize unwanted symptoms and ultimately lead to an increased likelihood of treatment success.

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- For Oregon Health Plan (OHP) Fee-For-Service (FFS) patients ***there are voluntary preferred anti-depressants to promote cost-effective choices***
- Bupropion, bupropion ER, mirtazapine, venlafaxine and generic SSRIs are cost-effective options for OHP FFS patients
- Giving antidepressants as a single dose once daily improves costs and increases adherence

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Bipolar Disorder: Resources for Primary Care Providers

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Mental illnesses are common conditions in the United States, and affect nearly 20% of the adult population.[1] Bipolar disorder affects 2.8% of adults yearly, and there is a 4.4% lifetime risk.[2] It occurs equally among adult men and women, and is slightly more common in adolescent girls than boys. Prevalence is highest in adults 18 to 29 years old and adolescents 17 to 18 years old.[2] Bipolar disorder has one of the highest rates of severe impairment of the mood disorders, over 80% of adults and nearly 90% of adolescents.[2] Individuals with bipolar disorder are at high suicide risk, and have the second highest suicide rate within 90 days of hospital discharge for patients with a psychiatric diagnosis.[3]

Bipolar disorder is characterized by distinct mood episodes which include shifts in mood, energy, activity levels, concentration, and functional capacity.[4] These episodes are distinctly differently from a patient's normal behavior and function at baseline. There are multiple types of bipolar disorder described in the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5), but patients are primarily categorized as bipolar I and bipolar II.[5] Bipolar I is characterized by having a manic episode, with or without a depressive episode, while bipolar II is characterized by depressive and hypomanic episodes without presence of manic episodes. The Mental Health Clinical Advisory Group (MHCAG), as part of the Oregon Health Authority (OHA) has recently completed publication of several care guides to assist clinicians with the diagnosis and care of individuals with bipolar disorder.[3,6-12] This newsletter will focus on the content of these care guides.

Differential Diagnosis

Several psychiatric conditions have overlapping symptoms with the depressive, hypomanic, and manic episodes seen in patients with bipolar disorder. Patients with bipolar disorder may be more likely to seek treatment when experiencing depression so it is also important to ask about symptoms of mania.[3] Hypomania may present before or after either manic or major depressive episodes.[3] Before diagnosis of bipolar disorder, other conditions which may present with symptoms of mania or hypomania should be considered and ruled out. Examples of other diagnoses to consider include schizoaffective disorder, schizophrenia, delusional disorder and, in the pediatric population, disruptive mood dysregulation disorder (DMDD).[9,13]

Differential diagnosis is further complicated by other mental health conditions that can present with an irritable mood. These include: depressive episodes, borderline personality disorder, post-traumatic stress disorder (PTSD), and attention-deficit/hyperactivity disorder (ADHD). A patient may have more than one of these conditions simultaneously, and substance intoxication or withdrawal can also mimic any of these states.[11] Co-occurring substance use disorders are common in patients with bipolar disorder. Delusions and hallucinations, racing thoughts, euphoria/elated mood, and grandiosity are key hallmark symptoms of mania that distinguish it from the other disorders.[11] **Table 1** differentiates mania from hypomania, with full symptom list available through MHCAG resources.[11]

Table 1: Differentiation of Mania and Hypomania[11]

Feature	Mania (Bipolar I)	Hypomania (Bipolar II)	NOT Bipolar Disorder
Energy/Activity	**Increased**	**Increased**	**Unchanged**
Number of associated symptoms*	3+ 4+ if mood only irritable	3+ 4+ if mood only irritable	< 3
Length of persistent symptoms	7+ days	4+ days	< 4 days **or** continuously for months or years
Psychotic symptoms	Maybe	No	
Change in function	Yes	Yes	
Functionally impairing	Yes	No	

*Symptoms of mania include: Inflated self-esteem, decreased sleep need, more talkative, flight of ideas/racing thoughts, distractibility, increased goal directed activity or psychomotor agitation, excessive involvement in activities with potential painful consequences. Symptoms present within episodes and differ from baseline.

Pharmacologic Therapy

Medication therapy during all phases of the disorder is a mainstay of bipolar treatment.[3] Initial treatment can vary depending on the patient's current symptoms at presentation (either manic or depressive symptoms). Those with severe disease, posing a safety risk to themselves or others, should be strongly considered for emergency department referral and/or inpatient treatment.[6,7]

Acute Mania

First-line therapy for mania should generally include lithium or quetiapine.[7] If a patient remains symptomatic despite first-line treatment, combination therapy should be considered. If combination therapy is ineffective, then generally patients should be switched to monotherapy with an alternative second generation antipsychotic in **Table 2**.[7]

Acute Depression

In addition to lithium and quetiapine, lamotrigine is recommended as first-line monotherapy treatment for patients presenting with bipolar depression.[6] Aripiprazole and monotherapy antidepressants should *never* be prescribed in acute bipolar depression. Both strategies are ineffective and antidepressants may trigger a manic or mixed episode.[6] If a patient with bipolar depression remains symptomatic despite first-line monotherapy, consider an alternative monotherapy or combination therapy in **Table 2**.[6]

Detailed treatment flowcharts[6,7] and side effect tables[12] are available from MHCAG to guide therapy decisions. All therapy should be tailored to individual patient's needs, with specific consideration for side effects, patient preference, symptom severity, and bipolar illness history. Maintenance therapy, usually with continuation of the pharmacotherapy used for stabilization, may continue for years or lifelong if tolerated and effective. Laboratory monitoring of serum levels (e.g. lithium and divalproex) and side effects should be more frequent in the first 6 months, then generally every 6 to 12 when stable and without new interacting medications.[6,7,12,14,15] Remember to include ammonia levels in patients on divalproex, particularly in those who appear to present with symptoms consistent with worsening depression.[14,16]

Consider consulting with specialists at the Oregon Psychiatric Access Line (OPAL) for patients with severe symptoms after initial combination therapy, or who remain symptomatic after 1 or 2 second-line treatments.[6,7] OPAL is a peer support resource available to primary care medical providers in Oregon and provides child and adult psychiatric phone consultations at no cost to clinicians.

Table 2. MHCAG Bipolar Medication Therapy Recommendations[6,7]

Acute Bipolar Mania		
1st Line Monotherapy	**1st line Combo therapy**	**2nd Line therapy**
Lithium **Quetiapine** **Temporary* lorazepam (anxiety or insomnia), olanzapine (agitation)**	Quetiapine+Lithium Quetiapine+Divalproex	Aripiprazole Asenapine Cariprazine Risperidone Ziprasidone
AVOID lamotrigine		
Acute Bipolar Depression		
1st Line Monotherapy	**2nd Line Monotherapy or Combo therapy**	
Lamotrigine **Lithium** **Quetiapine**	Cariprazine Divalproex Lurasidone	Lamotrigine+other bipolar tx med Lurasidone+Lithium Lurasidone+Divalproex Olanzapine+Fluoxetine SSRI+other bipolar tx med Bupropion+other bipolar tx med
AVOID Aripiprazole and antidepressant monotherapy		

Abbreviations: SSRI = selective serotonin reuptake inhibitor; tx = treatment.
*Generally limited to a few days and reserved for inpatient use

Certain patient populations, specifically women of childbearing potential, adolescents, and elderly patients require additional care with medication selection. Valproic acid and carbamazepine (CBZ) are contraindicated in pregnancy and use in women of childbearing potential should be avoided without effective birth control (BC) methods. Hormonal BC effectiveness is also reduced by CBZ. Hormonal BC may also lower the serum concentrations of lamotrigine and valproic acid; both should be monitored. Other first- and second-line treatments require caution or have insufficient safety data during pregnancy.[8] Young people may be more susceptible to metabolic side effects, and the lowest dose possible should always be used. Diagnosis is difficult in this population and should be confirmed before medication initiation.[8] Geriatric patients may see changes in their disease as they age, with more frequent, but less intense cycles. Be wary of polypharmacy and age-related changes in volume of distribution and metabolism, and increasing risk of cardiovascular disease with atypical antipsychotic use. If able, reduce doses or aim for the lower end of goal serum concentrations and monitor for age-related cognitive impairment.[8]

Co-occurring anxiety, ADHD, and substance use add complexity to bipolar treatment. If possible, use non-pharmacologic therapy to treat anxiety. If concurrent medication therapy is required, selective serotonin reuptake inhibitors (SSRIs) are likely safer than serotonin-norepinephrine reuptake inhibitors (SNRIs).[8] Tricyclic antidepressants (TCAs) should be considered contraindicated in bipolar disorder, as they have the highest risk of inducing mania.[3,8] Similarly, stimulants also confer risk of mania. If non-pharmacologic treatments are ineffective for ADHD, use the lowest effective stimulant dose, or consider atomoxetine or bupropion. These may have a lower risk of conversion to mania.[8] Clonidine or guanfacine may be other options for some patients. Substance use symptoms can mimic mania and depression, and increase a patient's risk of suicide.[3,8] If possible, clarify if symptoms of bipolar disorder were present during periods of sobriety and attempt to minimize substance-medication interactions.[8]

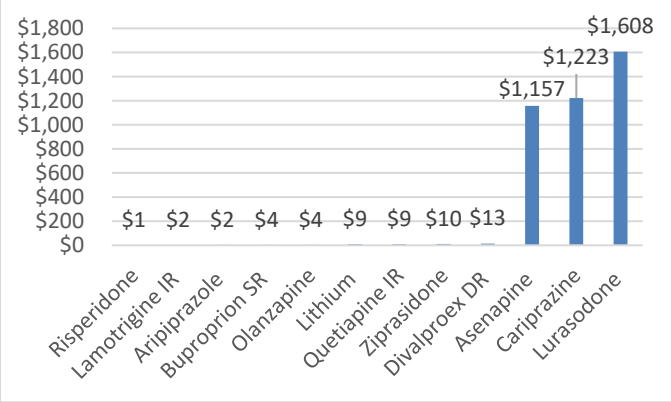
Non-pharmacological Therapy

In addition to pharmacologic therapy, psychosocial treatment, psychoeducation for the patient and patient supports, a regular sleep-wake cycle, and appropriately managing stress are key aspects of treatment for bipolar disorder. Certain psychotherapies, such as Interpersonal and Social Rhythm therapy in Bipolar I are considered evidence based and can reduce likelihood of recurrence.[17] Psychosocial needs should always be reassessed when breakthrough symptoms and lack of treatment effect are present.[3,6,7]

Comparative Costs

There are many medication options available to choose from, with generic products representing the best value. **Figure 1** illustrates the dramatic difference in 30-day supply average actual acquisition cost (AAAC) for various agents recommended in the treatment of bipolar disorder. Additionally, many brand name antipsychotic agents are priced the same for all strengths across the dosage spectrum ("flat-priced"). For those products, use of a single tablet to administer the total daily dose can result in significant medication savings compared to administration of multiple tablets to achieve the same daily dose (e.g. 40 mg, one tab Qday vs 20 mg, two tabs Qday).

Figure 1. Comparative Bipolar Monthly Cost for Select Agents



*Prices based on Myers and Stauffer Average Actual Acquisition Cost (AAAC) March 2, 2021. Available at:
https://www.mslc.com/uploadedFiles/Oregon/AACArchive/OHA%20Generic%20Web%20Listing_20210302_State.pdf
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Resources

Uncontrolled bipolar disorder causes severe impairment to the vast majority of patients with this condition. It also carries a high suicide risk. MHCAG resources[18] to assist on the diagnosis and treatment of this disorder can be found at: https://www.oregon.gov/oha/HPA/DSI-Pharmacy/Pages/MHCAG-Recommendations.aspxOPAL specialists are available to prescribing providers Monday-Friday 9am to 5pm at 503-346-1000.

- Many factors should be considered when choosing therapy for patients with acute bipolar depression or mania.
- Resources and specialists are available for patients with difficult to treat disease.
- Giving medications as the fewest number of daily tablets may decrease costs and increase adherence to therapy.

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Drug Class Update: SGLT-2 Inhibitors

Date of Review: August 2021

Date of Last Review: August 2020
Dates of Literature Search: 04/01/2020 - 05/17/2020

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

Purpose for Class Update:
There have been updated indications for drugs in the sodium-glucose cotransporter 2 (SGLT2) inhibitor class as well as additional literature published since the last review in August of 2020. The purpose of this update is to analyze the new evidence and update policy if needed.

Research Questions:
- In patients with type 2 diabetes (T2D), is there any new comparative efficacy or harms evidence for SGLT2 inhibitors (e.g., hemoglobin A1c [A1C], microvascular outcomes, macrovascular outcomes and mortality)?
- Are there subpopulations of patients with T2D for which SGLT2 inhibitors may be more effective or associated with less harm?

Conclusions:
- There were 2 new systematic reviews and meta-analyses, 5 randomized controlled trials, 2 new safety updates and 2 new indications identified in this review.
- There is moderate quality evidence that SGLT2 inhibitors reduce the risk of all-cause mortality, cardiovascular (CV) mortality and hospitalizations for heart failure (HF) in patients, irrespective of T2D diagnosis or HF diagnosis, based on evidence from 2 systematic reviews and meta-analyses.[1,2]
- The evidence for the use of SGLT2 inhibitors for reduction in risk of myocardial infarction (MI) is less robust, with analyses suggesting a modest benefit (hazard ratio [HR] 0.91; 95% confidence interval [CI], 0.84 to 0.99; p=0.03).[2]
- Subgroup analyses found that SGLT2 inhibitors were more effective than placebo in reducing all-cause mortality and CV mortality in patients with HF, independent of diabetes diagnosis, ejection fraction or renal function.[1]
- There was moderate quality of evidence that SGLT2 inhibitors are associated with a higher risks of diabetic ketoacidosis and genital infections, compared to placebo.[2]
- One randomized controlled trial (RCT) demonstrated modest quality evidence that empagliflozin was more effective than placebo at reducing CV death or hospitalization for HF in patients with and without diabetes (absolute risk reduction [ARR] 5.3%/number needed to treat [NNT] 19 over 16 months).[3]
- Ertugliflozin demonstrated no CV risk or benefit compared to placebo based on moderate evidence from one RCT.[4]

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- Dapagliflozin was more effective than placebo at reducing the risk of progression of chronic kidney disease (CKD) in patients, with and without diabetes, followed for a mean of 2.4 years based on moderate evidence (ARR 5.3%/NNT 19).[5] Findings led to an additional indication as described below.
- Moderate evidence demonstrated dapagliflozin was more effective than placebo (HR 0.74;95% CI, 0.65 to 0.85; ARR 4.9%/ NNT 21 over a median follow up of 18.2 months) at reducing the risk of worsening HF or death from CV causes in patients with and without diabetes with HF and reduced ejection fraction based on one RCT.[6] Findings led to an additional indication as described below.
- Canagliflozin reduced the risk of kidney failure and CV events more than placebo, 43.2 events per 1000 patient-years compared to 61.2 events per 1000 patient years, respectively, in patients with T2D and kidney disease, based on moderate evidence.[7]
- There was a new safety update for the SGLT2 class that warns of an increased risk of ketoacidosis after surgery. The recommendation is that SGLT2 inhibitors should be stopped at least 3-4 days (drug dependent) prior to surgery.[8]
- Prescribing information for canagliflozin was updated in August of 2020 to remove the boxed warning for increased risk of lower limb amputation.[9]

Recommendations:

- No changes to the preferred drug list (PDL) are warranted based on the evidence identified since the last review.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy:

- In August of 2020 a review was done to summarize findings from the Oregon Health and Science University (OHSU) Drug Effectiveness Review Project on Newer Diabetes Drugs and Cardiovascular Disease Outcomes. Findings from the report included literature up to October 2, 2019, which captured many trials related to the cardiovascular effects of SGLT2 inhibitors. Important findings were:
    - Canagliflozin, dapagliflozin, and empagliflozin reduced risks of hospitalization due to HF (NNT 42-80).
    - 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.
    - Canagliflozin reduced hemorrhagic stroke in patients with preexisting cerebrovascular disease (HR 0.43; 95% CI, 0.20 to 0.89; P=0.02).
- After executive session all the SGLT2 inhibitors as single agents (excluding combinations) were designated preferred with the exception of ertugliflozin.

Background:

SGLT-2 inhibitors modestly lower A1C, approximately -0.5% in placebo-controlled comparisons, in patients with T2D by increasing urinary glucose excretion.[10] They are used as a second-line pharmacotherapy option after metformin and lifestyle modifications. SGLT-2 inhibitors are unlikely to cause hypoglycemia and have modest benefits on blood pressure reduction and weight loss. There is also evidence of benefit on CV and renal outcomes in patients with and without diabetes (**Table 1**). While not all SGLT-2 inhibitors have been studied or demonstrated additional benefits beyond glucose lowering, the benefits are thought to be a class effect.

Table 1. Sodium-glucose Co-transporter 2 Inhibitors

Generic Name	Brand Name	Evidence for Use	Indications
Canagliflozin[9]	INVOKANA	- CKD in patients with T2DM - CV risk in patients with T2DM	- Improve glycemic control in adults with T2D - Reduce the risk of major CV events in adults with T2D and established CV disease

			- Reduce the risk of end-stage kidney disease in patients with T2D and diabetic nephropathy with albuminuria > 300 mg/day
Dapagliflozin[11]	FARXIGA	- CKD in patients with and without T2DM - CV risk in patients with T2DM - Reduced risk of HF in HFrEF patients with and without T2DM	- Improve glycemic control in adults with T2D - Reduce the risk of hospitalization for HF in patients with T2D and established CV disease or multiple CV risk factors - Reduce the risk of CV death and hospitalization for HF in adults with HF and HFrEF - Reduce the risk of eGFR decline and end-stage kidney disease CV death and hospitalization for HF in adults with CKD at risk of progression
Empagliflozin[12]	JARDIANCE	- CKD in patients without T2DM - CV risk in patients with T2DM - Reduced risk of heart failure in patients with and without T2DM	- Improve glycemic control in adults with T2D - Reduce the risk of CV death in adults with T2D and established CV disease
Ertugliflozin[13]	STEGLATRO	- Neutral CV effect	- Improve glycemic control in adults in adults with T2D
Abbreviations: CKD – chronic kidney disease; CV – cardiovascular; HFrEF – heart failure with reduced injection fraction; T2D – type 2 diabetes			

Common treatment emergent adverse events with SGLT-2 inhibitors include urinary tract infections, yeast infections, and foot ulcerations. It is not recommended to use SGLT-2 inhibitors in those at risk of diabetic ketoacidosis or those at risk of foot amputation.[10] SGLT-2 inhibitors should not be used in patients with an estimated glomerular filtration rate (eGFR) of < 60 mL/min/1.73 m^2 for ertugliflozin, < 45 mL/min/1.73 m^2 for dapagliflozin and empagliflozin or < 30 mL/min/1.73 m^2 for canagliflozin. Hypovolemia and acute kidney injury have been reported in patients taking diuretics and in the elderly. SGLT-2 inhibitors should be discontinued before any scheduled surgery to avoid risk of ketoacidosis (see **Table 7** below).

Outcomes used to validate efficacy of SGLT-2 inhibitors include A1C, mortality, hospitalizations, reduction in CV risk, reduction in CKD, hypoglycemia, genital infections, amputations, volume depletion and ketoacidosis.

The SGLT2 inhibitor class represents a modest expenditure to the Oregon Health Authority (OHA). There were 46 claims last quarter with 100% PDL compliance.

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:

Cardoso, et al – SGLT2 Inhibitors Decrease Cardiovascular Death and Heart Failure Hospitalizations in Patients with Heart Failure: A Systematic Review and Meta-analysis

A 2021 systematic review and meta-analysis analyzed the effect of SGLT2 inhibitors in patients with HF, without regard to diabetes diagnosis, on mortality and hospitalization endpoints. One author, of seven, had declared conflicts of interest.[1] Literature was searched through January 21, 2021, identifying 15 RCTs (n=20,241). The following medications were included in the review: canagliflozin (2 trials), dapagliflozin (4 trials), empagliflozin (6 trials), ertugliflozin (1 trial) and sotagliflozin (2 trials). All trials were placebo-controlled. Mean follow-up was 3 to 50.4 months.[1] Four studies included patients with heart failure with preserved ejection fraction (HFpEF) (left ventricular ejection fraction [LVEF] cutoffs varied from ≥45% to ≥50%). Risk of bias assessment demonstrated low risk of bias for all domains for all studies. Funnel plot analysis found no indication of publication bias.

Results of the systematic review and meta-analysis are presented in **Table 2.**[1] SGLT2 inhibitors were more effective than placebo for all outcomes studied. Subgroup analysis found a benefit of SGLT2 inhibitors compared to placebo in patients with diabetes (HR 0.74; 95% CI 0.68 to 0.80; p<0.0001) and in those without diabetes (HR 0.74; 95% CI, 0.63 to 0.86; p=0.0002).[1] There was also consistent benefit of SGLT2 inhibitors compared to placebo for estimated glomerular filtration rate (eGFR) <60 and eGFR ≥60, New York Heart Association (NYHA) class II or NYHA class III-IV, HFpEF and in those with reduced ejection fraction (EF). There were no significant differences between SGLT 2 inhibitors and placebo for the outcomes of amputations or bone fractures. More patients randomized to SGLT2 inhibitors experienced weight loss compared to those taking placebo (mean difference -1.11 kg; 95% CI, -1.41 to -0.82; p<0.0001).[1]

Table 2. Meta-analysis Finding of SGLT2 Inhibitors and Cardiovascular Death and Heart Failure[1]

Outcome	Results*	Interpretation
All-cause mortality	HR 0.86 (95% CI, 0.79 to 0.94); p = 0.0007	SGLT2 inhibitors were more effective than placebo in reducing all-cause mortality
Cardiovascular mortality	HR 0.86 (95% CI, 0.78 to 0.96); p = 0.006	SGLT2 inhibitors were more effective than placebo in reducing CV mortality
Hospitalizations for HF	HR 0.69 (95% CI, 0.62 to 0.76); p < 0.0001	SGLT2 inhibitors were more effective than placebo in reducing hospitalizations for HF
Urgent visits for HF	HR 0.39 (95% CI, 0.22 to 0.69); p = 0.001	SGLT2 inhibitors were more effective than placebo in reducing urgent visits for HR
Composite endpoint of CV mortality or hospitalizations for HF	HR 0.75 (95% CI, 0.70 to 0.80); p < 0.0001	SGLT2 inhibitors were more effective than placebo in reducing CV mortality or hospitalization for HF

Abbreviations: CI – confidence interval; CV – cardiovascular; HF – heart failure; HR – hazard ratio

Key: * Absolute risk reductions not available

Limitations to this review include no discussion of publication bias or risk of bias assessments. Additionally, all trials were graded as low risk of bias for all domains, which suggests potential bias since critical evaluation of the literature seldom results in these findings.

Salah, et al – Effect of Sodium-glucose Cotransporter 2 Inhibitors on Cardiovascular and Kidney Outcomes

A 2020 systematic review and meta-analysis analyzed the effect of SGLT2 inhibitors on CV and kidney outcomes in patients irrespective of diabetes diagnosis, patients with HF, and patients with chronic kidney disease.[2] The review methodology was clearly described and evidence was graded and assessed for risk of bias. Six of 11 authors had conflicts of interest. Literature was searched through September 24, 2020 which yielded 8 (n=59,747) randomized, placebo-controlled

trials.[2] Three trials evaluated dapagliflozin, 3 evaluated canagliflozin, 2 trials evaluated empagliflozin and one trial evaluated ertugliflozin. Two trials included patients with heart failure with reduced ejection fraction (HFrEF), irrespective of diabetes status, and 5 trials required a T2D diagnosis for inclusion.

Results for the systematic review and meta-analysis are presented in **Table 3**.[2] The overall quality of evidence was rated as moderate to high for all outcomes. The use of SGLT2 inhibitors in patients, with and without diabetes, was found to reduce the risk of adverse CV and kidney outcomes for all analyses except for stroke, in which there was no difference. In subgroup analyses of patients with T2D, with and without HF, the results were similar to those presented in **Table 3**. In patients with T2D and heart failure, the findings were also similar to those presented in **Table 3**, with the exception that there was no difference in the risk of stroke or MI between the two groups. There was no benefit in all-cause mortality, CV mortality, MI, or stroke for SGLT2 inhibitors for patients with T2D and no HF, although there was a decreased risk of hospitalizations for HF and reduction in the composite kidney outcome (end-stage kidney disease, a doubling of serum creatinine level, or kidney related mortality).[2] Patients with HF, irrespective of T2D diagnosis, had similar results to those presented in **Table 3**, with the exception of no risk reduction with SGLT2 inhibitors for the outcomes of MI and stroke. Patients with CKD (eGFR 60 mL/min/1.73 m^2 or less) found benefit with the use of SGLT2 inhibitors for reducing the risk of hospitalizations for heart failure, MI and reducing the reduction in the composite kidney outcome. Those patients that had no history of kidney disease (eGFR 60 mL/min/1.73 m^2 or greater) were found to have benefit from SGLT2 inhibitor therapy for the outcomes of reduction in the risk of hospitalization for HF and risk of experiencing the composite kidney outcome.

The risk of hypoglycemia or amputation with SGLT2 inhibitors was not statistically different from placebo. SGLT2 inhibitors demonstrated a risk of diabetic ketoacidosis in 0.23% of patients compared to 0.8% with placebo.[2] The risk of genital infections was also higher with SGLT2 inhibitors (OR 3.95; 95% CI, 3.01 to 5.18; moderate quality of evidence).[2]

Table 3. Meta-analysis Results for the Use of SGLT2 Inhibitors on Cardiovascular and Kidney Outcomes[2]

Outcome	Results	Quality of Evidence	Interpretation
All-cause mortality	HR 0.85 (95% CI, 0.78 to 0.91); p < 0.0001	Moderate	SGLT2 inhibitors were more effective than placebo at reducing all-cause mortality
Cardiovascular mortality	HR 0.84 (95% CI, 0.76 to 0.93); p = 0.007	Moderate	SGLT2 inhibitors were more effective than placebo at reducing CV mortality
Hospitalizations for HF	HR 0.69 (95% CI, 0.64 to 0.74); p < 0.00001	High	SGLT2 inhibitors were more effective than placebo at reducing hospitalizations for HF
Myocardial Infarction	HR 0.91 (95% CI, 0.84 to 0.99); p=0.03	High	SGLT2 inhibitors were slightly more effective than placebo at reducing risk of MI
Composite Kidney Outcome (end-stage kidney disease, a doubling of serum creatinine level, or kidney related mortality)	HR 0.62 (95% CI, 0.56 to 0.70); p=0.72	Moderate	SGLT2 inhibitors were more effective than placebo at reducing the risk of worsening composite kidney outcomes
Stroke	HR 0.98 (95% CI, 0.86 to 1.11); p<0.00001	High	There was no difference between SGLT2 inhibitors and placebo in the risk of stroke

Limitations to the review included no assessment of publication bias due to the inclusion of less than 10 trials, assessment of risk of bias but rated all domains as low, which suggests potential bias since critical evaluation of the literature seldom results in these findings.

After review, 25 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).[14–23, 24–33, 34–38]

New Guidelines:
High Quality Guidelines:
No new high quality guidelines were identified.

Additional Guidelines for Clinical Context:

ADA – Standards in Medical Care 2021
In 2021 the American Diabetes Association (ADA) updated guidance on the treatment of patients with T2D.[39] Due to lack of details on guideline methodology and a significant portion of the professional practice committee members having conflicts of interest with industry, the standards will not be reviewed in detail or relied upon for policy making decisions. The recommendations will be presented for clinical context. Recommendations were graded according to the evidence, ranging from level A (clear evidence based on RCTs), B (evidence from well conducted cohort studies), C (evidence from poorly controlled or uncontrolled trials) to E (expert consensus or clinical opinion).

Recommendations for the pharmacologic treatment of patients with T2D are presented in **Table 4**.[39] Pharmacotherapy should be initiated via a patient-centered approach to guide treatment selection. Metformin should be continued long-term and combined with additional therapies, including insulin, if needed. Metformin, used for glucose lowering, can be continued in patients with stable HF if eGFR remains >30 mL/min/1.73m^2. Metformin should not be used in patients who are unstable or hospitalized with heart failure. Medications should be re-evaluated every 3-6 months.

Table 4. ADA Pharmacotherapy Recommendations for Patients with Type 2 Diabetes[39]

Pharmacotherapy	Recommendation	Evidence Level
Metformin	- Preferred initial pharmacologic agent	A
Combination therapy	- Early initiation should be considered to extend time to treatment failure	A
Insulin	- Should be initiated if evidence of ongoing catabolism (weight loss), symptoms of hyperglycemia are present or when A1C levels (>10 %) or blood glucose levels (≥300 mg/dL) are very high	E
SGLT2 Inhibitors*	- Recommended for patients with established atherosclerotic CV disease or indicators of high risk, established kidney disease, or heart failure independent of A1C and in consideration of patient-specific factors. - Recommended for patients with established atherosclerotic CV disease, multiple atherosclerotic CV disease risk factors, or diabetic kidney disease to reduce the risk of major CV events and/or HF hospitalization	A

	- Recommended for patients with established HF with reduced ejection fraction is recommended to reduce the risk of worsening heart failure and CV death - Recommended for patients who have diabetic kidney disease for CV risk reduction when eGFR and urinary albumin creatinine are $\geq$ 30 mL/min/1.73m^2 or > 300 mg/g, respectively	
GLP-1 RAs*	- Recommended over insulin when possible - Recommended for patients with established atherosclerotic CV disease or indicators of high risk, established kidney disease, or heart failure independent of A1C and in consideration of patient-specific factors - Recommended for patients with established atherosclerotic CV disease or multiple atherosclerotic CV disease risk factors to reduce risk of major adverse CV events - Recommended for patients with CKD who are increased risk of CV events to reduce renal endpoints, primarily albuminuria, progression of albuminuria and CV events7	A
Abbreviations: CV – cardiovascular; eGFR – estimated glomerular filtration rate; GLP-1 RAs – glucagon-like peptide 1 receptor agonists; HF – heart failure; SGLT -2 – sodium glucose cotransporter-2 Key: * Select therapies with CV benefit (canagliflozin, dapagliflozin, empagliflozin, liraglutide, semaglutide, albiglutide, and dulaglutide)		

KDIGO – Diabetes Management in Chronic Kidney Disease

A 2020 update of the KDIGO guidelines for the management of patients with chronic kidney disease was published. Guideline methodology was clearly described and guideline development was patterned off of the AGREE II Checklist.[40] Chairs and working group members had conflicts of interest and the organization is funded by corporate sponsors so recommendations will be provided for clinical context. Recommendations were graded with a strength of recommendation and quality supporting evidence (**Table 5**). In addition to recommendations that are based on a systematic review and grading of the evidence, the guideline also includes “practice points” which are based on expert opinion.

Table 5. Description of KDIGO Recommendation Grading and Quality of Evidence Description[40]

NOMENCLATURE AND DESCRIPTION FOR RATING GUIDELINE RECOMMENDATIONS

Within each recommendation, the strength of the recommendation is indicated as **Level 1** or **Level 2**, and the quality of the supporting evidence is shown as **A**, **B**, **C**, or **D**.

	Implications		
Grade	**Patients**	**Clinicians**	**Policy**
Level 1 "We recommend"	Most people in your situation would want the recommended course of action, and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2 "We suggest"	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

Grade	**Quality of evidence**	**Meaning**
A	High	We are confident that the true effect is close to the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of effect is very uncertain, and often it will be far from the true effect.

Recommendations for glucose-lowering drugs are presented in **Table 6**.[40] Patients with T2D and CKD are candidates for treatment with metformin and a SGLT2 inhibitor, with metformin recommended first-line in patients that are treatment naïve. In patients taking metformin, the eGFR should monitored and if the eGFR is < 45 ml/min per 1.73 m^2 the dose should be divided in half (e.g., 500 mg twice daily). Patients with certain risk factors and an eGFR of 45-59 ml/min per 1.73 m^2 may be candidates for dose reduction. Patients receiving metformin for more than 4 years are at increased risk of vitamin B12 deficiency and should be monitored. Kidney function should be monitored annually and every 3-6 months in patients with an eGFR or 59 ml/min per 1.73 m^2 or less. SGLT2 inhibitors are recommended in preference to other glucose-lowering therapies besides metformin. Preference should be given to SGLT2 inhibitor with kidney or CV benefit. SGLT2 inhibitors can cause hypovolemia and ketosis and consideration should be given to discontinuing diuretics and temporary holding therapy in patients undergoing surgery, during prolonged fasting or with critically illness. Use of SGLT2 inhibitors should not occur in patients with kidney transplant. Choice of GLP-1 RA should be based on therapies with documented CV benefit. If exenatide is used, the patient should have a minimum CrCl of 30 ml/min.

Table 6. KIDGO Recommendations for Patients with Diabetes and Chronic Kidney Disease[40]

Recommendation	Strength of Recommendations	Quality of Evidence
Treat patients with T2D, CKD and an eGFR ≥30 ml/min per 1.73 m^2 with metformin	Level 1	B
Treat patients with T2D, CKD and an eGFR ≥30 ml/min per 1.73 m^2 with SGLT-2 inhibitors	Level 1	A
Patients not meeting glycemic targets with T2D, CKD taking metformin and an SGLT2 inhibitor, or who are not ablet to take them, long-acting GLP-1 RAs are recommended	Level 1	B
Abbreviations: CKD – chronic kidney disease; CrCl – creatinine clearance; eGFR – estimated glomerular filtration rate; SGLT-2 – sodium-glucose cotransporter-2; T2D – type 2 diabetes;		

After review, no guidelines were excluded due to poor quality.

New Formulations or Indications:

Dapagliflozin (Farxiga) – In April of 2021, dapagliflozin received an additional indication to reduce the risk of sustained eGFR decline, end-state kidney disease, CV death and hospitalization for HF in adults with chronic kidney disease at risk of progression (**Table 8** – DAPA-CKD).[7,11]

Dapagliflozin was also approved to reduce the risk of CV death and hospitalization for HF in adults with HF (NYHA class II-IV) with reduced ejection fraction in May of 2020 (**Table 8** – DAPA-HF).[6,11]

New FDA Safety Alerts:

Table 7. Description of new FDA Safety Alerts[8]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Canagliflozin*	INVOKANA	8/18/2020	Boxed Warning	Removal of warning for lower limb amputation and the removal of the albuminuria condition for continued dosing of patients whose eGFR falls between 30 and less than 45 mL/min/1.73 m^2
Canagliflozin*	INVOKANA	3/19/2020	Warnings and Precautions	Canagliflozin should be stopped at least 3 days prior to surgery to reduce the risk of developing ketoacidosis after surgery
Dapagliflozin*	FARXIGA	3/19/2020	Warnings and Precautions	Dapagliflozin should be stopped at least 3 days prior to surgery to reduce the risk of developing ketoacidosis after surgery
Empagliflozin*	JARDIANCE	3/19/2020	Warnings and Precautions	Empagliflozin should be stopped at least 3 days prior to surgery to reduce the risk of developing ketoacidosis after surgery
Ertugliflozin	STEGLATRO	3/19/2020	Warnings and Precautions	Ertugliflozin should be stopped at least 4 days prior to surgery to reduce the risk of developing ketoacidosis after surgery

Key: * Also applies to combination products

Randomized Controlled Trials:
A total of 34 citations were manually reviewed from the initial literature search. After further review, 29 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 5 trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 8. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Packer, et al[3] (EMPEROR-Reduced) MC, DB, PC, RCT, Phase 3 Median follow-up: 16 months	Empagliflozin 10 mg orally daily Vs. Placebo N = 3730	Patients with class, II, III, or IV HF and an ejection fraction of 40% or less	Composite endpoint of CV death or hospitalization for worsening heart failure	Empagliflozin: 361 (19.4%) Placebo: 462 (24.7%) HR 0.75 (95% CI, 0.65 to 0.86) P<0.001 ARR 5.3%/NNT 19 *Empagliflozin was more effective than placebo at reducing CV death or hospitalization for HF in patients with and without diabetes*
Cannon, et al[4] MC, DB, PC, NI, RCT, Phase 3 (VERTIS-CV) Mean follow-up: 3.5 years	Ertugliflozin 5 mg* orally once daily OR Ertugliflozin 15 mg* orally once daily OR Placebo orally once daily	Patients with T2DM and atherosclerotic CV disease N = 8246	Major CV events (composite of death from CV causes, nonfatal myocardial infarction or nonfatal stroke) Noninferiority margin was 1.3	Ertugliflozin: 653 (11.9%) Placebo: 327 (11.9%) HR 0.97; 95.6% CI, 0.85 to 1.11 P<0.001 for noninferiority *Ertugliflozin did not reduce or increase the risk of major CV events compared to placebo.*
Heerspink, et al[5] (DAPA-CKD) MC, DB, PC, RCT, Phase 3 Mean follow-up: 2.4 years	Dapagliflozin 10 mg orally once daily Vs. Placebo	Patients with CKD, with or without T2DM N = 4304	Composite of sustained decline in the estimated eGFR of at least 50%, end-stage kidney disease or death from renal or CV disease	Dapagliflozin: 197 (9.2%) Placebo: 312 (14.5%) HR 0.61 (95% CI, 0.51 to 0.72) P<0.001 ARR 5.3% / NNT 19 *Dapagliflozin was more effective than placebo at reducing the risk of progression of CKD in patients with and without diabetes*

McMurray, et al[6] (DAPA-HF) MC, DB, PC, RCT, Phase 3 Median follow-up: 18.2 months	Dapagliflozin 10 mg orally once daily Vs. Placebo * On standard heart failure drug therapy	Patients with NY Heart Association class II, III, or IV heart failure and an ejection fraction of 40% or less * 42% with diabetes N = 4744	Composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) 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 21 *Dapagliflozin was more effective than placebo at reducing the risk of worsening heart failure or death from CV causes in patients with and without diabetes*
Perkovic, et al[7] (CREDENCE) MC, DB, PC, RCT, Phase 3 Mean follow-up: 2.62 years	Canagliflozin 100 mg orally daily Vs. Placebo	Patients with T2D and albuminuric chronic kidney disease N = 4401	Composite of end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of <15 mL per minute per 1.73 m^2), doubling of serum creatinine level, or death from renal or CV causes	Canagliflozin: 245 (11%) Placebo: 340 (14%) HR 0.70 (95% CI, 0.59 to 0.82) P = 0.00001 *Canagliflozin reduced the risk of kidney failure and CV events more than placebo, 43.2 events per 1000 patient-years compared to 61.2 events per 1000 patient years, respectively, in patients with T2D and kidney disease*

Key: * Pooled results

Abbreviations: ARR = absolute risk reduction; CV = cardiovascular; DB = double-blind, GFR = glomerular filtration rate; HR = hazard ratio; MC = multi-center; NI = noninferiority; NNT = number needed to treat; NY = New York; PC = placebo controlled; RCT = randomized clinical trial; T2D = type 2 diabetes mellitus

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
canagliflozin	INVOKANA	TABLET	Y
dapagliflozin propanediol	FARXIGA	TABLET	Y
empagliflozin	JARDIANCE	TABLET	Y
canagliflozin/metformin HCl	INVOKAMET XR	TAB BP 24H	N
canagliflozin/metformin HCl	INVOKAMET	TABLET	N
dapagliflozin/metformin HCl	XIGDUO XR	TAB BP 24H	N
dapagliflozin/saxagliptin HCl	QTERN	TABLET	N
empaglifloz/linaglip/metformin	TRIJARDY XR	TAB BP 24H	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 Comparative Clinical Trials

Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes

Richard Pratley , Samuel Dagogo-Jack , James Mancuso , Susan Huyck , Urszula Masiukiewicz , Bernard Charbonnel , Robert Frederich , Silvina Gallo, Francesco Cosentino, Weichung J Shih, Ira Gantz, Steven G Terra, David Z I Cherney, Darren K McGuire, VERTIS CV Investigators

Background: The cardiovascular effects of ertugliflozin, an inhibitor of sodium-glucose cotransporter 2, have not been established.

Methods: In a multicenter, double-blind trial, we randomly assigned patients with type 2 diabetes and atherosclerotic cardiovascular disease to receive 5 mg or 15 mg of ertugliflozin or placebo once daily. With the data from the two ertugliflozin dose groups pooled for analysis, the primary objective was to show the noninferiority of ertugliflozin to placebo with respect to the primary outcome, major adverse cardiovascular events (a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke). The noninferiority margin was 1.3 (upper boundary of a 95.6% confidence interval for the hazard ratio [ertugliflozin vs. placebo] for major adverse cardiovascular events). The first key secondary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure.

Results: A total of 8246 patients underwent randomization and were followed for a mean of 3.5 years. Among 8238 patients who received at least one dose of ertugliflozin or placebo, a major adverse cardiovascular event occurred in 653 of 5493 patients (11.9%) in the ertugliflozin group and in 327 of 2745 patients (11.9%) in the placebo group (hazard ratio, 0.97; 95.6% confidence interval [CI], 0.85 to 1.11; P<0.001 for noninferiority). Death from cardiovascular causes or hospitalization for heart failure occurred in 444 of 5499 patients (8.1%) in the ertugliflozin group and in 250 of 2747 patients (9.1%) in the placebo group (hazard ratio, 0.88; 95.8% CI, 0.75 to 1.03; P = 0.11 for superiority). The hazard ratio for death from cardiovascular causes was 0.92 (95.8% CI, 0.77 to 1.11), and the hazard ratio for death from renal causes, renal replacement therapy, or doubling of the serum creatinine level was 0.81 (95.8% CI, 0.63 to 1.04). Amputations were performed in 54 patients (2.0%) who received the 5-mg dose of ertugliflozin and in 57 patients (2.1%) who received the 15-mg dose, as compared with 45 patients (1.6%) who received placebo.

Conclusions: Among patients with type 2 diabetes and atherosclerotic cardiovascular disease, ertugliflozin was noninferior to placebo with respect to major adverse cardiovascular events. (Funded by Merck Sharp & Dohme and Pfizer; VERTIS CV ClinicalTrials.gov number, NCT01986881.).

Dapagliflozin in Patients with Chronic Kidney Disease

Hiddo J L Heerspink, Bergur V Stefánsson, Ricardo Correa-Rotter, Glenn M Chertow, Tom Greene, Fan-Fan Hou, Johannes F E Mann, John J V McMurray , Magnus Lindberg, Peter Rossing, C David Sjöström, Roberto D Toto, Anna-Maria Langkilde, David C Wheeler, DAPA-CKD Trial Committees and Investigators

Background: Patients with chronic kidney disease have a high risk of adverse kidney and cardiovascular outcomes. The effect of dapagliflozin in patients with chronic kidney disease, with or without type 2 diabetes, is not known.

Methods: We randomly assigned 4304 participants with an estimated glomerular filtration rate (GFR) of 25 to 75 ml per minute per 1.73 m^2 of body-surface area and a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of 200 to 5000 to receive dapagliflozin (10 mg once daily) or placebo. The primary outcome was a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes.

Results: The independent data monitoring committee recommended stopping the trial because of efficacy. Over a median of 2.4 years, a primary outcome event occurred in 197 of 2152 participants (9.2%) in the dapagliflozin group and 312 of 2152 participants (14.5%) in the placebo group (hazard ratio, 0.61; 95% confidence interval [CI], 0.51 to 0.72; P<0.001; number needed to treat to prevent one primary outcome event, 19 [95% CI, 15 to 27]). The hazard ratio for the composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal causes was 0.56 (95% CI, 0.45 to 0.68; P<0.001), and the hazard ratio for the composite of death from cardiovascular causes or hospitalization for heart failure was 0.71 (95% CI, 0.55 to 0.92; P = 0.009). Death occurred in 101 participants (4.7%) in the dapagliflozin group and 146 participants (6.8%) in the placebo group (hazard ratio, 0.69; 95% CI, 0.53 to 0.88; P = 0.004). The effects of dapagliflozin were similar in participants with type 2 diabetes and in those without type 2 diabetes. The known safety profile of dapagliflozin was confirmed.

Conclusions: Among patients with chronic kidney disease, regardless of the presence or absence of diabetes, the risk of a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes was significantly lower with dapagliflozin than with placebo. (Funded by AstraZeneca; DAPA-CKD ClinicalTrials.gov number, NCT03036150.).

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

John J V McMurray, Scott D Solomon, Silvio E Inzucchi, Lars Køber, Mikhail N Kosiborod, Felipe A Martinez, Piotr Ponikowski, Marc S Sabatine, Inder S Anand , Jan Bělohlávek , Michael Böhm , Chern-En Chiang , Vijay K Chopra , Rudolf A de Boer , Akshay S Desai , Mirta Diez , Jaroslaw Drozdz , Andrej Dukát , Junbo Ge , Jonathan G Howlett , Tzvetana Katova , Masafumi Kitakaze , Charlotta E A Ljungman , Béla Merkely, Jose C Nicolau, Eileen O'Meara, Mark C Petrie, Pham N Vinh, Morten Schou, Sergey Tereshchenko, Subodh Verma, Claes Held, David L DeMets , Kieran F Docherty, Pardeep S Jhund, Olof Bengtsson, Mikaela Sjöstrand, Anna-Maria Langkilde , DAPA-HF Trial Committees and Investigators

Background: In patients with type 2 diabetes, inhibitors of sodium-glucose cotransporter 2 (SGLT2) reduce the risk of a first hospitalization for heart failure, possibly through glucose-independent mechanisms. More data are needed regarding the effects of SGLT2 inhibitors in patients with established heart failure and a reduced ejection fraction, regardless of the presence or absence of type 2 diabetes.

Methods: In this phase 3, placebo-controlled trial, we randomly assigned 4744 patients with New York Heart Association class II, III, or IV heart failure and an ejection fraction of 40% or less to receive either dapagliflozin (at a dose of 10 mg once daily) or placebo, in addition to recommended therapy. The primary outcome was a composite of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or cardiovascular death.

Results: Over a median of 18.2 months, the primary outcome occurred in 386 of 2373 patients (16.3%) in the dapagliflozin group and in 502 of 2371 patients (21.2%) in the placebo group (hazard ratio, 0.74; 95% confidence interval [CI], 0.65 to 0.85; P<0.001). A first worsening heart failure event occurred in 237 patients (10.0%) in the dapagliflozin group and in 326 patients (13.7%) in the placebo group (hazard ratio, 0.70; 95% CI, 0.59 to 0.83). Death from cardiovascular

causes occurred in 227 patients (9.6%) in the dapagliflozin group and in 273 patients (11.5%) in the placebo group (hazard ratio, 0.82; 95% CI, 0.69 to 0.98); 276 patients (11.6%) and 329 patients (13.9%), respectively, died from any cause (hazard ratio, 0.83; 95% CI, 0.71 to 0.97). Findings in patients with diabetes were similar to those in patients without diabetes. The frequency of adverse events related to volume depletion, renal dysfunction, and hypoglycemia did not differ between treatment groups.
Conclusions: Among patients with heart failure and a reduced ejection fraction, the risk of worsening heart failure or death from cardiovascular causes was lower among those who received dapagliflozin than among those who received placebo, regardless of the presence or absence of diabetes. (Funded by AstraZeneca; DAPA-HF ClinicalTrials.gov number, NCT03036124.).

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure
Milton Packer [1], Stefan D Anker [1], Javed Butler [1], Gerasimos Filippatos [1], Stuart J Pocock [1], Peter Carson [1], James Januzzi [1], Subodh Verma [1], Hiroyuki Tsutsui [1], Martina Brueckmann [1], Waheed Jamal [1], Karen Kimura [1], Janet Schnee [1], Cordula Zeller [1], Daniel Cotton [1], Edimar Bocchi [1], Michael Böhm [1], Dong-Ju Choi [1], Vijay Chopra [1], Eduardo Chuquiure [1], Nadia Giannetti [1], Stefan Janssens [1], Jian Zhang [1], Jose R Gonzalez Juanatey [1], Sanjay Kaul [1], Hans-Peter Brunner-La Rocca [1], Bela Merkely [1], Stephen J Nicholls [1], Sergio Perrone [1], Ileana Pina [1], Piotr Ponikowski [1], Naveed Sattar [1], Michele Senni [1], Marie-France Seronde [1], Jindrich Spinar [1], Iain Squire [1], Stefano Taddei [1], Christoph Wanner [1], Faiez Zannad [1], EMPEROR-Reduced Trial Investigators
Background: Sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of hospitalization for heart failure in patients regardless of the presence or absence of diabetes. More evidence is needed regarding the effects of these drugs in patients across the broad spectrum of heart failure, including those with a markedly reduced ejection fraction.
Methods: In this double-blind trial, we randomly assigned 3730 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less to receive empagliflozin (10 mg once daily) or placebo, in addition to recommended therapy. The primary outcome was a composite of cardiovascular death or hospitalization for worsening heart failure.
Results: During a median of 16 months, a primary outcome event occurred in 361 of 1863 patients (19.4%) in the empagliflozin group and in 462 of 1867 patients (24.7%) in the placebo group (hazard ratio for cardiovascular death or hospitalization for heart failure, 0.75; 95% confidence interval [CI], 0.65 to 0.86; P<0.001). The effect of empagliflozin on the primary outcome was consistent in patients regardless of the presence or absence of diabetes. The total number of hospitalizations for heart failure was lower in the empagliflozin group than in the placebo group (hazard ratio, 0.70; 95% CI, 0.58 to 0.85; P<0.001). The annual rate of decline in the estimated glomerular filtration rate was slower in the empagliflozin group than in the placebo group (-0.55 vs. -2.28 ml per minute per 1.73 m^2 of body-surface area per year, P<0.001), and empagliflozin-treated patients had a lower risk of serious renal outcomes. Uncomplicated genital tract infection was reported more frequently with empagliflozin.
Conclusions: Among patients receiving recommended therapy for heart failure, those in the empagliflozin group had a lower risk of cardiovascular death or hospitalization for heart failure than those in the placebo group, regardless of the presence or absence of diabetes. (Funded by Boehringer Ingelheim and Eli Lilly; EMPEROR-Reduced ClinicalTrials.gov number, NCT03057977.).

Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy
Vlado Perkovic [1], Meg J Jardine [1], Bruce Neal [1], Severine Bompoint [1], Hiddo J L Heerspink [1], David M Charytan [1], Robert Edwards [1], Rajiv Agarwal [1], George Bakris [1], Scott Bull [1], Christopher P Cannon [1], George Capuano [1], Pei-Ling Chu [1], Dick de Zeeuw [1], Tom Greene [1], Adeera Levin [1], Carol Pollock [1], David C Wheeler [1], Yshai Yavin [1], Hong Zhang [1], Bernard Zinman [1], Gary Meininger [1], Barry M Brenner [1], Kenneth W Mahaffey [1], CREDENCE Trial Investigators

Background: Type 2 diabetes mellitus is the leading cause of kidney failure worldwide, but few effective long-term treatments are available. In cardiovascular trials of inhibitors of sodium-glucose cotransporter 2 (SGLT2), exploratory results have suggested that such drugs may improve renal outcomes in patients with type 2 diabetes.
Methods: In this double-blind, randomized trial, we assigned patients with type 2 diabetes and albuminuric chronic kidney disease to receive canagliflozin, an oral SGLT2 inhibitor, at a dose of 100 mg daily or placebo. All the patients had an estimated glomerular filtration rate (GFR) of 30 to <90 ml per minute per 1.73 m^2 of body-surface area and albuminuria (ratio of albumin [mg] to creatinine [g], >300 to 5000) and were treated with renin-angiotensin system blockade. The primary outcome was a composite of end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of <15 ml per minute per 1.73 m^2), a doubling of the serum creatinine level, or death from renal or cardiovascular causes. Prespecified secondary outcomes were tested hierarchically.
Results: The trial was stopped early after a planned interim analysis on the recommendation of the data and safety monitoring committee. At that time, 4401 patients had undergone randomization, with a median follow-up of 2.62 years. The relative risk of the primary outcome was 30% lower in the canagliflozin group than in the placebo group, with event rates of 43.2 and 61.2 per 1000 patient-years, respectively (hazard ratio, 0.70; 95% confidence interval [CI], 0.59 to 0.82; P = 0.00001). The relative risk of the renal-specific composite of end-stage kidney disease, a doubling of the creatinine level, or death from renal causes was lower by 34% (hazard ratio, 0.66; 95% CI, 0.53 to 0.81; P<0.001), and the relative risk of end-stage kidney disease was lower by 32% (hazard ratio, 0.68; 95% CI, 0.54 to 0.86; P = 0.002). The canagliflozin group also had a lower risk of cardiovascular death, myocardial infarction, or stroke (hazard ratio, 0.80; 95% CI, 0.67 to 0.95; P = 0.01) and hospitalization for heart failure (hazard ratio, 0.61; 95% CI, 0.47 to 0.80; P<0.001). There were no significant differences in rates of amputation or fracture.
Conclusions: In patients with type 2 diabetes and kidney disease, the risk of kidney failure and cardiovascular events was lower in the canagliflozin group than in the placebo group at a median follow-up of 2.62 years. (Funded by Janssen Research and Development; CREDENCE ClinicalTrials.gov number, NCT02065791.).

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to May 17, 2021
Search Strategy:

#	Searches	Results
1	canagliflozin.mp. or Canagliflozin/	1344
2	dapagliflozin.mp.	1643
3	empagliflozin.mp.	1683
4	ertugliflozin.mp.	150
5	1 or 2 or 3 or 4	3720
6	limit 5 to (english language and humans and yr="2020 -Current")	383
7	limit 6 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	34

Appendix 4: Key Inclusion Criteria

Population	Patients with type 2 diabetes mellitus
Intervention	SGLT-2 inhibitors
Comparator	Placebo or active control
Outcomes	A1C, mortality, hospitalizations, reductions in CV or CKD risk
Setting	Outpatient

Appendix 5: 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/

Table 1. Approved Indications for SGLT2 Inhibitors

Drug Name	CV risk reduction in patients with T2D and established CV disease	Reduction in risk of end-stage kidney disease in patients with T2D and diabetic nephropathy with albuminuria >300 mg/day	Reduction in risk of eGFR decline and end-stage kidney disease CV death and hospitalization for HF in patients with CKD at risk of progression	HF risk reduction in patients with T2D and established CV disease or multiple CV risk factors	HF risk reduction in patients with HF and HFrEF
Canagliflozin	X	X			
Dapagliflozin			X	X	X

Empagliflozin	X				
Ertugliflozin					

Abbreviations: CKD – chronic kidney disease; CV – cardiovascular; eGFR – estimated glomerular filtration rate; HF – heart failure; HFrEF – heart failure with reduced ejection fraction; T2D – type 2 diabetes

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 and~~ qualify~~ies~~ for the requested therapy based on diagnoses and requirements~~the indications~~ in Table 1?	**Yes:** Go to #5	**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.~~
~~6.~~4. Does the patient have T2D and ~~Has the patient~~ failed, or have contraindications to, metformin or is requesting a SGLT2 inhibitor to be used in combination with metformin? (document contraindication, if any)	**Yes:** Go to #5~~7~~	**No:** Pass to RPh. Deny and recommend trial of metformin. See below for metformin titration schedule.

Approval Criteria		
~~7.~~5. 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 <30~~45~~ mL/min/ 1.73 m^2, or • Dapagliflozin and eGFR <25 ~~45~~ mL/min/ 1.73 m^2, or • Ertugliflozin and eGFR <30~~60~~ mL/min/ 1.73 m^2?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for up to 12 months

Renewal Criteria		
1. Is the request for the following treatments (including combination products) with associated renal function specifications ~~an associated estimated glomerular filtration rate (eGFR)~~: • Canagliflozin and ~~eGFR <30 mL/min/ 1.73 m^2~~ on dialysis, or • Empagliflozin and eGFR <30 ~~45~~ mL/min/ 1.73 m^2, or • Dapagliflozin and ~~eGFR <45 mL/min/ 1.73 m^2~~ on dialysis, or • Ertugliflozin and eGFR <30 ~~60~~ mL/min/ 1.73 m^2?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for up to 12 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: *8/21 (KS), 8/20 (KS), 6/20, 7/18, 9/17; 9/16; 3/16; 9/15; 1/15; 9/14; 9/13*
Implementation: *9/1/20; 8/15/18; 10/13/16; 2/3/15; 1/1/14*

Drug Use Research & Management Program
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Salem, Oregon 97301-1079
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New Drug Evaluation: casimersen, injection

Date of Review: August 2021
Generic Name: casimersen

End Date of Literature Search: April 12, 2021
Brand Name (Manufacturer): Amondys 45 (Sarepta Therapeutics, Inc)
Dossier Received: yes

Research Questions:

1. What is the evidence of efficacy (e.g., symptoms improvement, muscle or pulmonary function, quality of life, or disease progression) for casimersen in patients with Duchenne muscular dystrophy (DMD)?
2. What is the safety of casimersen for the treatment of patients with DMD?
3. Are there any subgroups (based on age, gender, ethnicity, comorbidities, disease duration or severity) that would benefit or be harmed from casimersen?

Summary of Prior Reviews and Current Policy

Therapies approved by the United States (US) Food and Drug Administration (FDA) for treatment of DMD (eteplirsen, golodirsen, viltolarsen, and deflazacort) were previously reviewed by the Pharmacy and Therapeutics (P&T) Committee in February 2021. In a previous review evaluated by the P&T Committee, there was insufficient evidence to evaluate differences in efficacy or safety between deflazacort and other corticosteroids for DMD or other conditions.[1,2] Evidence was limited by small sample sizes, high or unclear risk of bias, incomplete outcome reporting, and inadequate data in a population of US patients.[1,2] Current evidence demonstrates no difference in functional outcomes (e.g., distance traveled in 6 minutes) for eteplirsen or golodirsen compared to placebo. Evidence is significantly limited by high risk of bias and small sample sizes. Prior authorization (PA) is currently required for deflazacort and all target therapies for DMD to ensure medically appropriate use (see **Appendix 2**). Prednisone is available without PA.

Conclusions:

- There is no comparative efficacy or safety data for casimersen compared to other treatments for DMD.
- FDA approval was based on the secondary surrogate endpoint of an ongoing, unpublished, placebo-controlled, phase 3 trial of casimersen 30 mg/kg intravenously once weekly. An interim analysis in 43 children with DMD on concomitant chronic corticosteroids demonstrated a slight increase in dystrophin protein levels over 48 weeks with casimersen compared to baseline. Dystrophin levels were evaluated by Western blot and reported as a percent of normal levels. In patients treated with casimersen, dystrophin levels increased from baseline by 0.81% of normal (standard deviation [SD] 0.70) compared to an increase of 0.22% of normal (SD 0.49) in patients treated with placebo (mean difference (MD) of 0.59% between groups; 95% CI not reported; p=0.004).[3] It is not known if improvement in dystrophin correlates to clinical outcomes. There is currently no evidence that use of casimersen has any impact on symptoms, muscle or pulmonary function, quality of life, or disease progression in patients with DMD mutations amenable to exon 45 skipping. The trial is unpublished and risk of bias cannot be fully assessed.

Author: Sarah Servid, PharmD

- There is insufficient evidence to verify long-term safety of casimersen. Evidence is limited by the small population of patients which have been exposed to therapy. At the time of FDA approval, 59 patients had been on therapy for more than 48 weeks and only 19 patients had been on therapy for more than 120 weeks.[3] Patients with markers of severe disease (e.g., patients unable to complete baseline functional tests, with severe pulmonary disease or left ventricular ejection fraction less than 50%) were excluded from clinical trials.[3] Like other targeted therapies for DMD, casimersen labeling includes warnings for renal adverse events, and due to the intravenous route of administration, there is possible risk of serious infections related to use of indwelling catheters, particularly in patients receiving chronic corticosteroids.[4]

Recommendations:

- Update prior authorization (PA) criteria for DMD to include casimersen.

Background:

Duchenne muscular dystrophy (DMD) is a rare X-linked genetic disorder caused by the absence of a functional dystrophin protein. DMD primarily affects males and is the most common type of muscular dystrophy with an estimated worldwide prevalence of 1.7 to 4.2 in 100,000 patients.[5] In the US, it is estimated that Duchenne and Becker muscular dystrophies may affect 1.4 to 2 in 10,000 males ages 5 to 9 years,[5,6] and the estimated incidence of new DMD patients is 1 in approximately 5000 male births.[7] Patients with DMD experience progressive muscle deterioration leading to loss of ambulation and decreased muscle strength. Long-term complications include respiratory failure, dilated cardiomyopathy, arrhythmias, and increased risk for thrombotic events. In many patients, these complications can lead to wheelchair dependence by age 12 and death at an early age.[5] In a recent systematic review assessing median survival of patients with DMD, improved trends in survival over time were identified which was attributed to improvements in care, including use of ventilator support, leading to a decrease in respiratory-associated deaths in this population.[8] Age of death in patients in earlier decades (e.g., 1960s-1970s), was significantly earlier than age of death for patients who died in more recent decades.[8] The pooled median survival was 29.9 years (95% CI 26.5 to 30.8) in patients with ventilator support compared to 19 years (95% CI 18 to 20.9) in patients without ventilator support.[8]

There is currently no curative treatment for DMD, and therapy focuses on improving symptoms, enhancing quality of life, and decreasing disease progression. Guidelines from the American Academy of Neurology recommend initiation of corticosteroids, either deflazacort or prednisone, as first-line treatment for ambulatory children with a decline in motor function to delay loss of ambulation, preserve pulmonary function, and reduce risk of scoliosis.[5,9] Corticosteroids are often continued if patients become non-ambulatory, though the continued benefits are less clear with progressive disease.[5] Other non-pharmacological therapies which are often essential in disease management include physical therapy and use of support devices such as braces and wheelchairs.[5] As the disease progresses, mechanical ventilation and spinal surgery may be used to improve pulmonary function and decrease pain from scoliosis and vertebral fractures.[5]

Recent new therapies approved for DMD include targeted, exon-skipping therapies. The theoretical goal of these therapies is to modify mRNA splicing and increase the amount of dystrophin protein in cells, thereby correcting the underlying disease process. Using this mechanism, a truncated dystrophin protein is formed. While preclinical animal studies indicate truncated dystrophin can be functional, the level of function associated with the truncated protein is unknown and may vary depending on the inherited mutation.[10] Targeted therapies are approved for specific mutations that are amenable to exon skipping. Eteplirsen was approved in 2016 for DMD with mutations amenable to exon 51 skipping. Approximately 13% of patients with DMD are thought to have mutations amenable to exon 51 skipping.[11] In 2019 and 2020, golodirsen and viltolarsen were approved for patients with mutations amenable to exon 53 skipping (thought to represent about 8% of the DMD population or approximately 1200 patients in the US).[12] Most recently, casimersen was approved for patients with mutations amenable to exon 45 skipping. All therapies have the same mechanism of action and are administered as weekly intravenous infusions.

These therapies have been approved based on changes in dystrophin protein. While eteplirsen and golodirsen have shown a slight increase in dystrophin (<1% of normal dystrophin levels), the impact of these therapies on clinical outcomes had not been demonstrated in randomized controlled trials.[13,14] In the trial used for eteplirsen approval (n=12), there was no difference observed in the 6-minute walk test (6MWT) at 24 or 48 weeks compared to placebo. While subsequent follow-up studies have evaluated pulmonary, cardiac, and muscle function in this population, they are limited by their single-arm observational design, small sample size, and lack of comparator groups or comparison to historical control.[15-18] Similarly, there are no published, placebo-controlled studies evaluating functional outcomes with golodirsen, and FDA review of available clinical outcomes identified no substantial difference from natural history data.[12] Confirmatory post-marketing, randomized trials have yet to be completed for either therapy.

There is currently no consensus on the minimum change in dystrophin level that may result in a clinical improvement, and available thresholds cited in the literature are currently based on expert opinion. In untreated patients with DMD, documented dystrophin levels typically range from 0 to 0.4% of normal healthy patients.[19] Experts suggests that dystrophin levels less than 3% of normal are typically associated with a phenotype of DMD.[19] Some experts suggest that very minimal improvements in dystrophin level may constitute a beneficial change while others suggest that dystrophin levels at 10-20% of normal would likely correlate to clinically significant changes in muscle symptoms or function.[19,20] In patients with Becker muscular dystrophy, a less severe form of muscular dystrophy, dystrophin protein levels are on average 80% of normal.[19] An FDA analysis evaluating the change in 6MWT per year and dystrophin level changes associated with golodirsen failed to demonstrate a positive correlation (R=0.14), indicating that small increases in a truncated dystrophin protein may not be an adequate surrogate marker for functional improvement.[12]

Clinically important outcomes in DMD include morbidity, mortality, disease progression, motor function, and improvements in motor, pulmonary, or cardiac symptoms. There are multiple methods used assess motor function and strength in patients with DMD including timed functional tests scoring tools. For example, the North Star Ambulatory Assessment (NSAA) is a 17-item scale designed for patients able to ambulate at least 10 meters (total score range 0 to 34).[21,22] It evaluates various functional assessments including standing, hopping, climbing stairs, and rising from the floor. Individual items are rated on a 0 to 2 scale based on ability to perform the test normally (2), able to perform the test with modifications or assistance (1), and inability to perform the test (0). The minimum clinically important difference in NSAA score has not been established. Other standard timed functional tests include time to climb 4 stairs, time to walk 10 meters, time required to stand from a prone position, and the 6MWT which evaluates distance traveled in 6 minutes.[23] In healthy children less than 7 years of age, the distance patients are able to walk is expected to remain stable or improve over time with estimated mean walk distances ranging from 500-700 meters.[18,24,25] The minimum clinically important difference in the 6MWT for patients with DMD is approximately 30 meters.[23] NSAA scores less than 16 are more often correlated with 6MWT of less than 300 meters and scores greater than 30 correlate moderately with 6MWT of more than 400 meters.[22] The NSAA is generally considered a more comprehensive measure of functional status compared to other functional outcomes, but the score is often very dependent on patient effort.[19] Pulmonary function is often evaluated during clinical trials using spirometry. In patients with DMD, current evidence demonstrates a gradual decline in pulmonary function tests beginning around 5 years of age (about 4-7% per year of percent predicted forced vital capacity [FVC] and peak expiratory flow [PEF]).[26,27] However, there is currently only limited data to correlate decline in percent predicted FVC or PEF to clinical outcomes such as need for mechanical ventilation or airway clearance.[26]

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

Clinical Efficacy:
Casimersen was approved based on interim results from a single, ongoing, unpublished, double-blind, multicenter, placebo-controlled phase 3 study (NCT02500381).[4] The primary endpoint in the ongoing study is change in the 6MWT from baseline to 96 weeks, but FDA approval was based on changes in dystrophin protein from baseline to 48 weeks, a secondary study endpoint. The study is projected to enroll 111 patients eligible for exon 45 skipping with expected completion in 2023. Forty-three patients had dystrophin results available for interim analysis by the FDA. Eligible patients were 7 to 13 years of age, had mutations amenable to exon 45 skipping, and were on a stable dose of corticosteroids.[3] Patients were required to have be ambulatory with a 6MWT between 300 and 450 meters, have stable pulmonary function with FVC of at least 50% of predicted, and have a left ventricular ejection fraction (LVEF) greater than 50% which limits applicability in patients with progressive or severe disease.[3]

As the study is unpublished, risk of bias cannot be assessed. However, there were documented differences in baseline characteristics between groups including slight differences in dystrophin at baseline, time since diagnosis, and duration of steroid use. Dystrophin level at baseline was 0.93% of normal (SD 1.67) for patients treated with casimersen and 0.54% of normal (SD 0.79) for patients treated with placebo.[3] Patients randomized to placebo also had, on average, a shorter time since diagnosis (by 3 months) and a longer duration of steroid use (by 6 months).[3] Differences in baseline characteristics can increase risk of selection bias and decrease certainty regarding whether the observed results are truly related to a treatment effect. It is currently unclear how these differences may impact study outcomes.

Dystrophin levels were evaluated by Western blot at 48 weeks and were reported as a percent of normal levels. Dystrophin level increased from baseline by 0.81% of normal (SD 0.70) in patients treated with casimersen and by 0.22% of normal (SD 0.49) in patients treated with placebo (MD of 0.59% between groups; 95% CI not reported; p=0.004).[3] Other analyses to evaluate the amount of exon 45 skipping by RT-PCR demonstrated more exon skipping with casimersen therapy and were used to support the primary analysis. Several sensitivity analyses were performed by the FDA and produced results consistent with the primary analysis.[3] Sensitivity analyses excluded several outlier patients with large dystrophin levels at baseline, and evaluated dystrophin levels above and below the lower limit of quantification were.[3]

Similar to other targeted therapies for DMD, the clinical benefit of casimersen has yet to be determined. Currently, there are no data available to evaluate clinical outcomes of functional status, symptom improvement, disease progression, or impact on quality of life. Additionally, it is unclear whether improvements in dystrophin correlate to clinical outcomes, and there is no consensus on what difference in dystrophin may be clinically significant. Though it is difficult to make comparisons between trials due to differences in populations, genotypes, and variability in methods used for evaluation of dystrophin, the small magnitude of dystrophin improvement for casimersen appears to be similar to change in dystrophin observed with other targeted therapies for DMD.[2]

Clinical Safety:
At the time of approval, 76 patients were included in the safety dataset for casimersen. Fifty-nine patients had been on therapy for more than 48 weeks and only 19 patients had been on therapy for more than 120 weeks.[3] The most common adverse events associated with treatment included upper respiratory tract infections, cough, pyrexia, headache, arthralgia and oropharyngeal pain (**Table 1**). Adverse events which occurred in 10% to 20% of the population, and were more commonly reported than placebo, included ear pain, nausea, ear infection, post-traumatic pain, and dizziness.

Table 1. Common Adverse events occurring in more than 20% of treated patients and at least 5% more frequent than placebo[4]

Adverse reaction	Casimersen (n=27)	Placebo (n=16)
Upper respiratory tract infection	65%	55%
Cough	33%	26%
Pyrexia	33%	23%
Headache	32%	19%
Arthralgia	21%	10%
Oropharyngeal Pain	21%	7%

Serious adverse events occurred in 17 patients (22%), the most common being fractures and rhabdomyolysis.[3] Three serious adverse events associated with presence of an indewelling port were documented in a single patient (bacteremia, septic embolus, and vena cava thrombosis).[3] Rhabdomyolysis occurred in 2 patients (6%) treated with placebo compared to 4 patients (7%) treated with casimersen.[3] Most patients experiencing rhabdomyolysis had identifying triggers known to be associated with rhabdomyolysis in patients with DMD including moderate to vigorous physical exercise and exposure to sevoflurane, a general anesthetic. One patient treated with casimersen experienced rhabdomyolysis and cardiac arrest subsequent to general anesthesia and surgery for a central venous port placement.[3]

Like other oligonucleotides for DMD, casimersen labeling includes warnings for serious renal adverse reactions based on data from non-clinical studies. No serious renal adverse events were observed in clinical studies, though more treatment emergent adverse events suggestive of renal injury occurred with casimersen treatment (including increased urine protein/creatinine ratio [n=1] and proteinuria [n=5]), compared to none in the placebo group.[3] Additionally, more patients treated with casimersen had a positive urine dipstick above 1+ compared to placebo.[3]

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

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Functional or symptom improvement (motor, pulmonary, or cardiovascular)
2) Quality of life
3) Disease progression
4) Mortality
5) Serious adverse events
6) Study withdrawal due to an adverse event

Primary Efficacy Endpoint:
1) Dystrophin protein production

Table 2. Pharmacology and Pharmacokinetic Properties.[4]

Parameter	
Mechanism of Action	binds to Exon 45 of the dystrophin pre-mRNA, resulting in exclusion of this exon during mRNA processing and producing an internally truncated dystrophin protein
Oral Bioavailability	N/A (administered intravenously)
Distribution and Protein Binding	8.4% to 31.6% protein binding (not concentration-dependent) Vd = 367 mL/kg at steady state
Elimination	Plasma clearance 180 mL/hr/kg > 90% excreted unchanged in the urine
Half-Life	3.5 hours (SD 0.4)
Metabolism	N/A

Abbreviations: kg= kilograms; L=liters; N/A = not applicable; Vd = volume of distribution; SD = standard deviation

Table 3. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. NCT02500381 FDA Summary Review[3] Phase 3, DB, PC, MC RCT	1. casimersen 30 mg/kg/ week IV 2. placebo 48 weeks Interim results reported at 48 weeks 96 week double blind treatment phase followed by 48 week open-label phase	Demographics: - Mean age: 9 yrs - White: 86% - Mean (SD) dystrophin 1. 0.93% (SD 1.67) 2. 0.54% (SD 0.79) - Weight ≥median 1. 13 (48%) 2. 9 (56%) - Mean BMI: 1. 19.3 kg/m^2 (SD 4.1) 2. 18.8 kg/ m^2 (SD 4.4) - Months since diagnosis 1. 68 (SD 36) 2. 65 (SD 35) - Months of steroid use: 1. 43 (SD 22) 2. 49 (SD 27) - Corticosteroid: 74% deflazacort - Corticosteroid frequency daily: 86% Key Inclusion Criteria: - Age 7-13 yrs - DMD amenable to exon 45 skipping - Stable steroid dose in prior 6 months - Stable cardiovascular therapy in the prior 12 wks - Mean 6MWT between 300 and 450m - Stable pulmonary function with FVC≥50% predicted Key Exclusion Criteria: - LVEF <50% - Need for nocturnal ventilation - QT_C ≥450 msec - Major surgery or changes to the physical therapy regimen within the prior 3 months - Other clinically significant illness	Interim Analysis 1. 27 2. 16	Primary Endpoint: Change in 6MWT from baseline: NR Secondary Endpoints: Change from Baseline in Dystrophin Protein Levels Determined by Western Blot at 48 weeks 1. 0.81% (SD 0.70) 2. 0.22% (SD 0.49) 1 vs. 2: 0.59%; p=0.004 Other secondary clinical outcomes were not reported including ability to rise independently from the floor, time to loss of ambulation, change in the NSAA from baseline, and change in the forced vital capacity percent predicted from baseline	NA	SAE NR DC due to AE: 0%	NA for all	**Risk of Bias (low/high/unclear)**: FDA approval was based on an interim analysis of a secondary endpoint. Interim results are unpublished and the study is ongoing (with estimated completion date in 2023). Risk of bias cannot be fully assessed. **Applicability**: Patient: Patients were ambulatory and able to complete all baseline functional assessments. Patients with acute illness or cardiomyopathy were excluded limiting applicability in patients with severe disease. All enrolled patients were on stable therapy with a corticosteroid, the current standard of care for DMD. The majority of enrolled patients were white, limiting applicability for other races and ethnicities. Intervention: Weekly doses of 4 mg/kg to 30 mg/kg were evaluated in an early phase I/II trial of 12 participants, but treatment response by dose was not assessed.[28] All enrolled patients were prescribed first-line therapy with corticosteroids; there is limited evidence for efficacy or magnitude of benefit when administered without corticosteroids. Comparator: Placebo appropriate to determine efficacy. Outcomes: The outcome evaluated in this interim analysis is a surrogate marker and it has not yet been correlated with functional outcomes. There is no agreement on what level of dystrophin may result in a clinically important improvement. Setting: This ongoing study is currently recruiting patients in the US, Australia, Canada, multiple European countries, Israel, and Russia.

Abbreviations [alphabetical order]: 6MWT = 6 minute walk test; AE = adverse events; ARR = absolute risk reduction; BMI = body mass index CI = confidence interval; DC = discontinuation; DMD = Duchenne muscular dystrophy; FDA = Food and Drug Administration; LVEF = left ventricular ejection fraction; MC = multicenter; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = non-significant; NSAA = North Star Ambulatory Assessment; RCT = randomized controlled trial; SAE = serious adverse events; SD = standard deviation; wks = weeks; yrs = years

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AMONDYS 45 safely and effectively. See full prescribing information for AMONDYS 45.

AMONDYS 45 (casimersen) injection, for intravenous use
Initial U.S. Approval: 2021

INDICATIONS AND USAGE

AMONDYS 45 is an antisense oligonucleotide indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 45 skipping. This indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with AMONDYS 45 *[see Clinical Studies (14)]*. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials. (1)

DOSAGE AND ADMINISTRATION

- Serum cystatin C, urine dipstick, and urine protein-to-creatinine ratio should be measured before starting AMONDYS 45 (2.1)
- 30 milligrams per kilogram of body weight once weekly (2.2)
- Administer as an intravenous (IV) infusion over 35 to 60 minutes via an in-line 0.2 micron filter (2.2, 2.4)
- Dilution required prior to administration (2.3)

DOSAGE FORMS AND STRENGTHS

Injection: 100 mg/2 mL in a single-dose vial (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Kidney Toxicity: Based on animal data, may cause kidney toxicity. Kidney function should be monitored; creatinine may not be a reliable measure of renal function in DMD patients. (5.1, 13.2)

ADVERSE REACTIONS

The most common adverse reactions (incidence >20% and at least 5% higher than placebo) were upper respiratory tract infection, cough, pyrexia, headache, arthralgia, and oropharyngeal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sarepta Therapeutics, Inc. at 1-888-SAREPTA (1-888-727-3782) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 2/2021

Appendix 2: Prior Authorization Criteria

Drugs for Duchenne Muscular Dystrophy

Goal(s):

- Encourage use of corticosteroids which have demonstrated long-term efficacy.
- Restrict use of targeted oligonucleotides for exon skipping and deflazacort to patients with Duchenne Muscular Dystrophy.
- Limit use of deflazacort to patients with contraindications or serious intolerance to other oral corticosteroids.

Length of Authorization:

- 6 months

Requires PA:
- Targeted therapies for exon skipping (see Table 1; pharmacy or physician administered claims)
- Deflazacort

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

Table 1. FDA Approved Indications for targeted therapies

Drug	Indication	Examples of amenable mutations (list is not all inclusive)
casimersen (Amondys 45®)	Duchenne muscular dystrophy with mutations amenable to exon 45 skipping	Deletion of exons 44, 46, 46 to 47, 46 to 48, 46 to 49, 46 to 51, 46 to 53, 46 to 55, or 46 to 57
eteplirsen (Exondys 51®)	Duchenne muscular dystrophy with mutations amenable to exon 51 skipping	Deletion of exons 43 to 50; 45 to 50; 47 to 50; 48 to 50; 49 to 50; 50; or 52
golodirsen (Vyondys 53®)	Duchenne muscular dystrophy with mutations amenable to exon 53 skipping	Deletion of exons 42 to 52; 45 to 52; 47 to 52; 48 to 52; 49 to 52; 50 to 52; 52; or 54 to 58
Viltolarsen (Viltepso®)	Duchenne muscular dystrophy with mutations amenable to exon 53 skipping	Deletion of exons 42 to 52; 45 to 52; 47 to 52; 48 to 52; 49 to 52; 50 to 52; 52; or 54 to 58

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for treatment of Duchenne Muscular Dystrophy?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness. Note: Therapies are not indicated for other forms of muscular dystrophy or other diagnoses.
3. Is the request for deflazacort?	**Yes:** Go to #4	**No:** Go to #7

Approval Criteria		
4. Is the patient ≥ 2 years of age?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Has the patient received, or have contraindications to, all routine immunizations recommended for their age? Note: Routine vaccinations for patients at least 2 years of age typically include hepatitis B, hepatitis A, diphtheria, tetanus, pertussis, pneumococcal conjugate, inactivated poliovirus, influenza, and at least 2 doses of measles, mumps, rubella, and varicella.	**Yes:** Go to #6 Document physician attestation of immunization history.	**No:** Pass to RPh. Deny; medical appropriateness.
6. Does the patient have a documented contraindication or intolerance to oral prednisone that is not expected to crossover to deflazacort? Note: deflazacort may be an option for patients with clinically significant weight gain associated with prednisone use.	**Yes:** Approve for up to 12 months. Document contraindication or intolerance reaction.	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of prednisone.
7. Is the request for continuation of treatment previously approved by FFS?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #8
8. Is the request for an FDA-approved indication (Table 1)?	**Yes:** Go to #9 Document genetic testing.	**No:** Pass to RPh, Deny; medical appropriateness.
9. Is the request for golodirsen or viltolarsen?	**Yes:** Go to #10	**No:** Go to #12
10. Is the request for combination treatment with 2 or more targeted therapies (e.g., golodirsen and viltolarsen)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #11

Approval Criteria		
11. Has the provider assessed baseline renal function as recommended in the FDA label? ~~Golodirsen: documented glomerular filtration rate as evaluated by a 24 hour urine collection within the past 3 months~~ ~~Viltolarsen:~~ Recommended monitoring includes serum cystatin C, urine dipstick, and urine protein-to-creatinine within the past 3 months	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness.
12. Has the patient been on a stable dose of corticosteroid for at least 6 months or have documented contraindication to steroids?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness.
13. Has baseline functional assessment been evaluated using a validated tool (e.g., the 6-minute walk test, North Star Ambulatory Assessment, etc)?	**Yes:** Document baseline functional assessment and approve for up to 6 months	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the request for golodirsen or viltolarsen?	**Yes:** Go to #2	**No:** Go to #3
2. Has the provider assessed renal function? Golodirsen: Recommended monitoring includes proteinuria monthly and serum cystatin C every three months. If results are abnormal, a 24H urine collection should be performed. Viltolarsen or casimersen: Recommended monitoring includes urine dipstick monthly, serum cystatin C every 3 months, and protein-to-creatine ratio every 3 months.	**Yes:** Go to #3	**No:** Pass to RPh, Deny; medical appropriateness.

Renewal Criteria		
3. Has the patient's baseline functional status been maintained at or above baseline level or not declined more than expected given the natural disease progression?	**Yes:** Go to #4 Document functional status and provider attestation.	**No:** Pass to RPh, Deny; medical appropriateness.
4. Is there documentation based on chart notes of any serious adverse events related to treatment (e.g., acute kidney injury, infections, etc.)?	**Yes:** Go to #5	**No:** Approve for up to 6 months
5. Has the adverse event been reported to the FDA Adverse Event Reporting System (FAERS)?	**Yes:** Approve for up to 6 months Document provider attestation	**No:** Pass to RPh, Deny; medical appropriateness.

P&T/DUR Review: *8/21 (SS); 2/21; 6/20; 09/19; 11/17; 07/17*
Implementation: *3/1/21; 7/1/20; 11/1/19; 1/1/18; 9/1/17*

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Prior Authorization Criteria Update: Belimumab

Purpose of Update:

- To review new evidence for the safety and efficacy of belimumab for treatment of adults with active lupus nephritis who are receiving standard therapy.

The FDA approved an expanded indication for the use of belimumab in adults with active lupus nephritis March 2021.[1] Belimumab was initially approved for treatment of patients aged 5 years and older with active, autoantibody-positive systemic lupus erythematosus (SLE).[1] Patients with acute, severe lupus nephritis were excluded from the initial phase 3 clinical trials which led to FDA approval of belimumab. Lupus nephritis, which occurs in 25 to 60% of patients with SLE, is the most common severe manifestation of SLE and a major cause of illness and death.[2]

The expanded indication for lupus nephritis was based on a phase 3, multinational, multicenter, randomized double-blind placebo-controlled trial.[3] A total of 448 patients were enrolled in the trial and randomized 1:1 to belimumab or placebo. Belimumab was dosed at 10 mg per kg, administered intravenously on Days 0, 14, 28, and then every 28 days in addition to standard therapy. Standard therapy included: corticosteroids with 1) oral mycophenolate mofetil (MMF) for induction followed by MMF for maintenance, or 2) intravenous cyclophosphamide for induction followed by oral azathioprine for maintenance.[3] Patients were required to be at least 18 years old, with autoantibody-positive SLE and biopsy-proven, active lupus nephritis. International Society of Nephrology and Renal Pathology Society (ISN/RPS) lupus nephritis classifications are presented in **Table 1**. At screening, the patients had a ratio of urinary protein to creatinine of 1 or more and ISN/RPS biopsy-proven class III, IV, or V lupus nephritis within 6 months before, or during, screening.[3] Patients who had been on dialysis within the last year or with severe renal impairment (estimated glomerular filtration rate [eGFR] less than 30 ml/minute/1.73 m^2) were excluded from randomization.[3]

Table 1. ISN/RPS Lupus Nephritis Classifications[4]

Status	Description
Class I	Minimal mesangial lupus nephritis: earliest and mildest form of glomerular involvement
Class II	Mesangial proliferative lupus nephritis: excellent prognosis and no specific therapy is indicated
Class III	Focal lupus nephritis: patients present with hematuria and proteinuria, possibly to also have hypertension, decreased renal function and/or nephrotic syndrome. Light microscopy reveals less than 50 percent of glomeruli are affected.
Class IV	Diffuse lupus nephritis: patients present with hematuria and proteinuria and frequently seen with hypertension, decreased renal function and nephrotic syndrome. Light microscopy reveals more than 50 percent of glomeruli are affected.
Class V	Lupus membranous nephropathy: patients present with signs of nephrotic syndrome
Class VI	Advanced sclerosing lupus nephritis: patients present with slowly progressive kidney dysfunction associated with proteinuria

The trial was conducted at 107 sites located in Asia (47% of trial sites), North America (17%), South America (16%), and Europe (19%).[3] Mean patient age was 33 years (range: 18 to 77); the majority (88%) were female and Asian (50%).[3] Over half of the patients (58%) has Class III or IV lupus nephritis.[3] GlaxoSmithKline contributed to the design, data collection, and data analysis of the trial.

The primary endpoint was a composite assessment of primary efficacy renal response (PERR) at week 104, defined as a ratio of urinary protein to creatinine less than or equal to 0.7, an eGFR no worse than 20% below pre-flare value or greater than or equal to 60 ml/minute/1.73m^2 of body surface area (BSA), and no use of glucocorticoid rescue therapy for treatment failure.[3] Secondary endpoints included complete renal response (CRR) at week 104 (a ratio of urinary protein to creatinine of less than 0.5, an eGFR that was no worse than 10% below the pre-flare value or greater than or equal to 90 ml/minute/1.73 m^2 BSA, and no use of rescue therapy), PERR at week 52, and the time to a renal-related event or death.[3] At week 104, 43% (n=96) of the belimumab group versus 32% (n=72) of the placebo group had a PERR response (odds ratio [OR] 1.6, 95% confidence interval [CI] 1.0 to 2.3, p=0.03).[3] At week 104, more patients who received belimumab had a CRR compared to those who received placebo (30% vs. 20%, respectively; OR 1.7, 95% CI 1.1 to 2.7, p=0.02).[3] At week 52, 47% (n=104) of the belimumab group and 20% (n=79) of the placebo group had a PERR (OR 1.6, 95% CI 1.1 to 2.4, p=0.02).[3] The group of patients who received belimumab had a significantly lower risk of a renal-related event or death during the trial than the group of patients who received placebo (hazard ratio, 0.51; 95% CI, 0.34 to 0.77; P=0.001).[3] These results were primarily because of increased proteinuria, impaired kidney function, or both (in 17 patients in the belimumab group and 39 patients in the placebo group) or kidney-related treatment failure (in 16 and 20 patients, respectively).[3] One death from any cause was observed in the belimumab group compared with 2 in the placebo group.[3] There were no new safety events identified in this trial compared to previous trials of belimumab.[3]

Black patients with lupus nephritis are more likely to have a worse prognosis than those in other racial groups.[3] This study enrolled a low proportion of Black patients (14%), which limits applicability of study results to Black patients. Black patients who received belimumab appeared to be more likely to have a PERR and a CRR at week 104 than those who received placebo.[3] However, in both groups, the percentage of Black patients who had a response was lower than the percentage of patients in the overall population who had a response.[3] Other trial limitations were the low percentage of patients receiving cyclophosphamide–azathioprine (27%) compared with mycophenolate (73%).[3] Only two induction and maintenance regimens were permitted as background therapy, although additional therapies for lupus nephritis, such as calcineurin inhibitors, are currently used in practice.[3] In addition, patient-reported outcomes were not included.[3]

Recommendation:

- Update the prior authorization criteria for belimumab to include the expanded FDA indication for treatment of adults with active lupus nephritis.

References:

1. Belimumab (BENLYSTA) Package Insert. Philidelphia, PA: GlaxoSmithKline, March 2021.
2. Hanly JG, O'Keeffe AG, Su L, et al. The frequency and outcome of lupus nephritis: results from an international inception cohort study. *Rheumatology (Oxford)*. Feb 2016;55(2):252-62. doi:10.1093/rheumatology/kev311.
3. Furie R, Rovin BH, Houssiau F, et al. Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis. *New England Journal of Medicine*. 2020;383(12):1117-1128..
4. Bajema IM, Wilhelmus S, Alpers CE, et al. Revision of the International Society of Nephrology/Renal Pathology Society classification for lupus nephritis: clarification of definitions, and modified National Institutes of Health activity and chronicity indices. *Kidney Int.* 2018;93(4):789-796.

Belimumab (Benlysta®)

Goal(s):

- Promote use that is consistent with national clinical practice guidelines and medical evidence.

Length of Authorization:

- 6 months

Requires PA:

- Benlysta® (belimumab) 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 ICD-10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Does the patient have severe active central nervous system lupus?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #4
4. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #5

Approval Criteria		
5. Is the patient either: a) diagnosed with lupus nephritis and aged 18 years or older? OR b) Is the patient diagnosed with systemic lupus erythematosus (SLE) and aged 5 years or older?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is belimumab dosed appropriately and with an approved formulation for patient's age as outlined in Table 1?	**Yes:** Go to # 7	**No:** Pass to RPh. Deny; medical appropriateness
76. Is the patient currently on other biologic therapy or intravenous cyclophosphamide?	**Yes:** Pass to RPh. Deny; medical appropriateness. Belimumab has not been studied in combination with other biologics or intravenous cyclophosphamide.	**No:** Go to # 87
87. Is the drug being prescribed by or in consultation with a rheumatologist, nephrologist, or a provider with experience treating SLE or lupus nephritis?	**Yes:** Go to # 98	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
98.Does the patient have active autoantibody-positive SLE or lupus nephritis and is a baseline assessment of SLE disease activity available using one of the following functional assessment tools: • SLE Index Score (SIS) • British Isles Lupus Assessment Group (BILAG) • Systemic Lupus Activity Measure (SLAM) • Systemic Lupus Erythematosus Disease Activity Score (SLEDAI) • Physicians Global Assessment (PGA) • Systemic Lupus International Collaborating Clinic (SLICC) Damage Index • Urinary protein to creatinine ratio • Most recent estimated Glomerular Filtration Rate (eGFR)	**Yes:** Go to # 109. Document baseline assessment _____.	**No:** Pass to RPh. Deny; medical appropriateness
109. Is the patient currently receiving standard of care treatment for Systemic Lupus Erythematosus (SLE) or lupus nephritis e.g., hydroxychloroquine, systemic corticosteroids, non-steroidal anti-inflammatory drugs, azathioprine, mycophenolate, or methotrexate?	**Yes:** Approve for 6 months.	**No:** Pass to RPh. Deny; medical appropriateness. Belimumab has not been studied as monotherapy in patients with SLE.

Renewal Criteria		
1. Is the patient currently on other biologic therapy or intravenous cyclophosphamide?	**Yes:** Pass to RPh. Deny; medical appropriateness. Belimumab has not been studied in combination with other biologics or intravenous cyclophosphamide.	**No:** Go to #2

Renewal Criteria		
2. Has the patient's SLE disease activity improved or stabilized as assessed by one of the following functional assessment tools: • SLE Index Score (SIS) • British Isles Lupus Assessment Group (BILAG) • Systemic Lupus Activity Measure (SLAM) • Systemic Lupus Erythematous Disease Activity Score (SLEDAI) • Physicians Global Assessment (PGA) • Systemic Lupus International Collaborating Clinic (SLICC) Damage Index • Urinary protein to creatinine ratio • eGFR	**Yes:** Approve for 6 months.	**No:** Pass to RPh; Deny; medical appropriateness.

Table 1: FDA approved ages

Indication	Approved formulation	
	Intravenous (IV) powder for solution	**Subcutaneous (SC) Injection**
Systemic Lupus Erythematosus (SLE)	5 years and older	18 years and older
Lupus Nephritis	18 years and older	18 years and older
IV (usual dosage): 10 mg/kg IV infusion over 1 hour every 2 weeks for the first 3 doses, then every 4 weeks thereafter **SC** (usual dosage): **SLE**: 200 mg SC once weekly **Lupus Nephriti**s:400 mg (two 200-mg injections) SC once weekly into abdomen or thigh for 4 doses, then 200 mg SC once weekly thereafter		

P&T/DUR Review: *8/21 (DM) 2/20 DM, 5/18 (DM)*
Implementation: *3/1/2020; 7/1/18*

Drug Use Research & Management Program
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Drug Class Update with New Drug Evaluation: Other Dyslipidemia Drugs

Date of Review: August 2021

Generic Name: Evinacumab-dgnb

Date of Last Review: August 2020
Dates of Literature Search: 05/31/2020 – 06/01/2021
Brand Name (Manufacturer): Evkeeza™ (Regeneron)
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 evinacumab 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 evinacumab in patients with familial hypercholesterolemia, 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 high quality evidence that alirocumab and evolocumab decrease the risk of cardiovascular disease (CVD) and myocardial infarction (MI) compared to placebo in patients with CVD or at high CV risk with a modest absolute risk difference of 1-2%.[1] There is high quality evidence that alirocumab also decreases all-cause mortality compared to placebo (absolute risk difference of 1%). There is low quality evidence of no consistent benefit on CV outcomes or all-cause mortality with either alirocumab or evolocumab compared to ezetimibe and statins.
- There remains insufficient evidence evaluating alirocumab or evolocumab in lower CV risk patients, and long-term efficacy and safety beyond 3 years is lacking.

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- There is high quality evidence that alirocumab significantly reduces LDL-C compared to placebo in adults with homozygous familial hypercholesterolemia (HoFH) on background statin therapy with a percent change reduction from baseline at week 12 of -26.9% versus 8.6%. There is insufficient evidence that alirocumab reduces risk of CVD or mortality in patients with HoFH. [2]
- There is moderate quality evidence that omega-3 fatty acids 4 grams per day over 3 years does not reduce CV outcomes compared to corn oil in high CV risk patients on stable statin therapy. [3]
- There is high quality evidence based on one study with a high magnitude of benefit that evinacumab significantly reduces LDL-C compared to placebo at 24 weeks (-47% vs. 2%, respectively; difference -49%; 95% Confidence Interval [CI] -65% to -33.1%) in adults with homozygous familial hypercholesterolemia (HoFH) on maximally tolerated lipid lowering therapy. [4] However, there is no data evaluating evinacumab on clinical outcomes, including CV events, CV mortality and all-cause mortality. Data in pediatric and elderly patients are insufficient.
- There is insufficient evidence evaluating the efficacy and safety in patient with other causes of hypercholesterolemia, including those with heterozygous familial hypercholesterolemia (HeFH).
- Evinacumab is associated with hypersensitivity reactions and is considered teratogenic. It should not be used in pregnancy. The overall study sample is small and currently lacks adequate safety data to detect additional adverse events.

Recommendations:

- Due to its unknown benefit on CV outcomes and limited use to HoFH, make evinacumab non-preferred and include prior authorization to limit utilization to patients with HoFH requiring additional LDL-lowering on maximally tolerated lipid lowering therapies.
- Evaluate comparative costs in executive session.

Summary of Prior Reviews and Current Policy

- Current PA polices for PCKS9 inhibitors, bempedoic acid 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).[5]
- 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.[6] 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%).[7]
- 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).[8]

- 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.
- 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.

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.[9] 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. [9]

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.[10] 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.[5] 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.[10] Additionally, a moderate-intensity statin was used as the study comparator, which is not consistent with current practice recommendations.[5]

Evolocumab (Repatha®) and alirocumab (Praluent®) are subcutaneously injected human monoclonal antibodies that reduce LDL-C by inhibiting PCSK9.[11, 12] 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 in patients with 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).**[8, 11 7] 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 in patients with elevated triglycerides despite statin

therapy.[6] Icosapent ethyl gained FDA approval as an add-on therapy to reduce CV events for adults with elevated triglycerides (≥ 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. [6]

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.[13] 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.[14]

Table 1: Characteristics of Cardiovascular Outcome trials for Non-statins[5-8]

	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 216 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[5-8]

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

Evinacumab is a fully human monoclonal antibody approved for homozygous familial hypercholesteremia (HoFH). HoFH is a rare genetic condition affecting an estimated 200-300 patients in the United States. [15] The genetic mutation causes changes in LDL-C processing and ineffective plasma clearance of LDL-C, resulting in persistent, severe hyperlipidemia (> 400 mg/dl) beginning in childhood and premature CV disease and death. The most common mutations (90%) involve

both alleles of the LDL receptor. Current treatment consists of standard LDL-C lowering therapy with statins, PCSK9 inhibitors and ezetimibe. Apheresis is reserved for individuals who do not respond to first-line treatments. Evinacumab was granted Breakthrough Therapy designation for the treatment of HoFH based on preliminary evidence from a phase 2 trial.[16] It is the first treatment to reduce LDL-C independent of the LDL receptor. This is theoretically advantageous in HoFH since many patients do not have functional LDL receptors and are more difficult to treat with conventional 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.

Systematic Reviews:
After review, 13 systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses),[17-20] wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), drug (not FDA approved)[21] or outcome studied (e.g., LDL-C).[22, 23 24-29]

- A Cochrane Collaboration systematic review aimed to evaluate the effectiveness and safety of PCSK9 inhibitors for prevention of CVD.[1] RCTs with at least 24 weeks of follow-up comparing alirocumab or evolocumab to placebo or active treatments were included. The primary efficacy outcomes were composite endpoint of CVD, all-cause mortality, MI, and stroke. Twenty-four studies were included (n=60,997). Eighteen trials included alirocumab and six trials included evolocumab. [1] All but one study, were industry-sponsored, multicenter trials and the majority included patients with either established CVD or high CV risk. Most of the trials had low or unclear risk of bias. Four studies were open-label and had high risk of performance bias and detection bias, and 7 studies had high risk of attrition bias.

  There was high certainty evidence (10 studies) that, compared to placebo, alirocumab decreased the risk of CVD (absolute risk difference [RD] -2%; OR 0.87; 95% CI 0.80-0.94), mortality (RD -1%; OR 0.83; 95% CI 0.72 to 0.96), and MI (RD -2%; OR 0.86; 95% CI 0.79 to 0.94). [1] There was low-certainty evidence, few supporting studies, and a small absolute difference between alirocumab and active treatment (ezetimibe and/or statins for CVD (RD 1%; OR 1.37; 95% CI 0.65 to 3.87) and mortality (RD -1%; OR 0.51; 95% CI 0.18 to 1.40) demonstrating no significant benefit. [1] Results were consistent for evolocumab compared to placebo with high-certainty evidence for a reduction in CVD (RD -2%; OR 0.84; 95% CI 0.78 to 0.91) and MI (RD -1%; OR 0.72; 95% CI 0.64 to 0.82) with slightly smaller absolute difference and fewer supporting studies. [1] There was no significant difference in all-cause mortality (OR 1.04; 95% CI 0.91 to 1.19) with evolocumab compared to placebo. Compared to active treatment (ezetimibe and/or statins), there was low-certainty evidence with a small absolute difference with evolocumab on CVD (RD <1%; OR 0.66; 95% CI 0.14 to 3.04), MI (RD <1%; OR 0.66; 95% CI 0.23 to 1.85) and mortality (RD < 1%; OR 0.43; 95% CI 0.14 to 1.30) with no clear decreased risk. [1] Evidence was rated as low certainty based on low number of events and open-label treatment allocation.

The authors concluded that there is strong evidence supporting PCSK9 inhibitors for those not eligible for other lipid-lowering therapies or who cannot meet their lipid goals despite standard treatments, but the evidence base comparing PCSK9 inhibitors with ezetimibe and statins is much weaker and it remains unknown if these agents can be used as replacement therapies. Furthermore, the absolute risk reduction remains small (often less than 1%) for all clinical outcomes. Evidence regarding PCSK9 inhibitors for treatment of people at low risk remains uncertain and long-term efficacy and safety beyond 3 years is lacking. There is very limited evidence overall on any potential safety issues of evolocumab and alirocumab.

- The Institute for Clinical and Economic Review (ICER) evaluated bempedoic acid with or without ezetimibe and inclisiran in the treatment of HeFH.[30] Since inclisiran has not been FDA approved, this review will focus on the findings for bempedoic acid. The authors of this review compared the efficacy, safety and effectiveness of bempedoic acid to maximally tolerated lipid-lowering therapy (placebo arm). A pairwise meta-analysis for primary and secondary outcomes was conducted. Five Phase III RCTs including bempedoic acid were included. LDL-C was the primary outcome for all included trials. [30] Three of the studies were good quality based on the United States Preventive Services Task Force (USPSTF) criteria and two were fair quality because of differential loss to follow-up. The authors found a significant reduction in LDL-C from baseline with bempedoic acid compared to placebo in patients on maximally tolerated lipid lowering therapy (difference -19.5%; 95% CI -22.7 to -16.4; $p<0.0001$; $I^2=69\%$) with high heterogeneity due to different populations studied and differences in the intervention and comparison group. [30] There are insufficient data evaluating bempedoic acid on clinical outcomes. A five-year ongoing clinical outcome study is expected to be completed in 2022. However, all-cause mortality and CV outcomes were included in the safety analysis in two studies. An analysis of this data found nonsignificant increases in all-cause mortality (RR 2.25; 95% CI 0.76 to 6.67) and CV mortality (RR 1.52; 95% CI 0.41 to 5.70) and decreases in non-fatal MI (RR 0.54; 95% CI 0.25 to 1.15) and major adverse cardiovascular events (MACE) (RR 0.79; 95% CI 0.58 to 1.07). [30] Number of events were very small for all outcomes and results are imprecise. There was a slightly higher incidence of serious adverse events and discontinuations due to adverse events with bempedoic acid compared to placebo in all trials. The most common events that led to discontinuation were diarrhea, muscle related events, elevated liver enzymes and headache.

New Guidelines:
No new high-quality guidelines identified.

New Formulations or Indications:
In April 2021, alirocumab was FDA approved as an adjunct to other LDL-C lowering therapies in adults with HoFH to reduce LDL-C.[31] Approval was based on data from the ODYSSEY HoFH trial (**Table 3).** [2] Previous FDA labeling included patients with established CVD and HeFH. The ODYSSEY HoFH trial demonstrated a significant reduction in LDL-C in adults with HoFH on background statin therapy (97%) compared to placebo. There is no data evaluating CV outcomes or all-cause mortality in HoFH. There were no differences in serious adverse events and no discontinuations due to adverse events in either group.

New FDA Safety Alerts:
No new FDA Safety Alerts

Randomized Controlled Trials:
A total of 13 citations were manually reviewed from the initial literature search. After further review, 8 citations were excluded because of wrong study design (e.g., observational, post-hoc analysis)[32-35], comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical)[36.37-39] Trials identified which evaluated evinacumab are included below. The remaining 3 trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 3. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
ODYSSEY HoFH[2] MC, PC, PG, DB, RCT	Alirocumab 150 mg SC Q 2 weeks vs. placebo 12 weeks	Adults with HoFH and LDL-C ≥70 mg/dl on background statin therapy or intolerance (n=69)	Percent change in LDL-C from baseline to week 12	<u>% Change in LDL-C:</u> Alirocumab: -26.9% Placebo 8.6% Difference -35.6 (95% CI -51.2% to -19.9%) P<0.0001
STRENGTH[3] DB, MC, RCT	Omega-3 fatty acids (carboxylic acid formulation) 4gm/day vs. matching corn oil 3 years	Adults at high risk for CV event on statin therapy (n=33,047)	Composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, and hospitalization for unstable angina	<u>CV Composite outcome:</u> Omega-3: 785 (12%) Corn Oil: 795 (12.2%) HR 0.99; 95% CI 0.90 to 1.09
Prespecified analysis of ODYSSEY OUTCOMES RCT[40]	Alirocumab versus placebo	Adults with recent ACS on maximally tolerated statin (n=18,924)	PAD and VTE events	<u>PAD Events:</u> Alirocumab: 101 (1.1%) Placebo: 145 (1.5%) HR 0.69; 95% CI 0.54 to 0.89 <u>VTE events:</u> Alirocumab: 37 (0.4%) Placebo: 55 (0.6%) HR 0.67; 95% CI 0.44 to 1.01

Abbreviations: ACS: acute coronary syndrome; CV = cardiovascular; DB=double blind; HoFH: homozygous familial hypercholesteremia; HR = hazard ratio; LDL-C: low density lipoprotein cholesterol; MC = multicenter; MI = myocardial infarction; PAD = peripheral artery disease; PC= placebo controlled; PG = parallel group; RCT = randomized controlled trial; SC= subcutaneous; VTE= venous thromboembolism

<u>NEW DRUG EVALUATION:</u> Evinacumab (Evkeeza)

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:
Evinacumab is a fully human recombinant monoclonal antibody that inhibits angiopoietin-like 3 (ANGPTL3), an enzyme involved in lipid metabolism. Inhibition of ANGPTL3 allows enhanced lipoprotein lipase activity, resulting in a reduction in LDL-C independent of the LDL-C receptor. It is indicated as an adjunct to other LDL-C lowering therapies for the treatment of adult and pediatric patients aged 12 years and older, with homozygous familial hypercholesterolemia (HoFH).[41]

It was FDA approved based on a single 24-week double-blinded, multicenter, placebo-controlled, randomized trial in adult and adolescent patients with HoFH as defined by genotyping or clinical criteria, LDL-C ≥70 mg/dL, and on maximally tolerated lipid lowering therapy **(Table 6).**[4] Lipid lowering therapy was defined as daily statin, ezetimibe, and a PCSK9 inhibitor. The genetic diagnosis included a variant in two *LDLR* alleles or the presence of variants in apolipoprotein B (APOB) or PCSK9. Clinical criteria were defined as total cholesterol > 500 mg/dl with or without the presence of xanthomas. A single trial was considered acceptable by FDA due to the rarity of HoFH and the magnitude of effect with evinacumab compared to placebo.[15] After an 8-week run-in period for genotyping and stabilization of background lipid lowering therapy, patients were randomized 2:1 to receive evinacumab 15 mg/kg intravenously (IV) every 4 weeks or placebo.[4] The primary outcome was the percent reduction from baseline to Week 24 in calculated LDL-C.

Patients treated with evinacumab experienced a 47% reduction in LDL-C compared to an increase by 2% in the placebo group (difference -49%; 95% CI -65 to -33.1).[4] The difference was observed as early as Week 4. The absolute change from baseline in calculated LDL-C was -134.7 mg/dl with evinacumab and -2.6 mg/dl with placebo. Fifty-six percent of patients on evinacumab had a 50% or greater reduction from baseline LDL compared to 5% on placebo (OR 24.2; 95% CI 3 to 195.6).[4] However, this finding was imprecise with an extremely wide confidence interval. There were no obvious effects on LDL-C lowering ability based on HoFH mutation, baseline LDL-C or background lipid lowering therapy. Patients in the evinacumab also had significantly lower levels of apolipoprotein B, non-HDL cholesterol and total cholesterol compared to those in the placebo group. Patients were entered in a 48-week open-label extension study after completion of the 24-week double-blinded period. Efficacy was maintained from 24 weeks to 48 weeks in those previously treated with evinacumab.[15]

Risk of bias was low to unclear. Given the small sample size, there were differences in baseline characteristics between the two groups. More patients with null-null LDL-receptor variants (< 15% activity) were in the evinacumab group (35%) compared to placebo (27%), which is expected to be a more difficult to treat population. There was a higher baseline LDL-C in evinacumab compared to placebo (260 mg/dl vs. 247 mg/dl) and more individuals 65 years of age and older in the evinacumab group (19%) compared to placebo (0%). There were also imbalances in background lipid lowering therapy between groups, with 70% of patients in the evinacumab group on at least three lipid lowering therapies and only 50% in the placebo group.

Only 2 pediatric patients were randomized and enrolled. The clinical diagnostic criteria used for enrollment was more liberal than typically used in practice (total cholesterol > 500 mg/dl vs. LDL-C > 500 mg/dl). Therefore, the trial likely included patients with less severe disease than what would be seen in practice. Older patients and pediatric patients were poorly represented in the study, and it is difficult to generalize results to these populations. The FDA review notes that an additional 11 pediatric participants were enrolled in an ongoing open-label study. Efficacy and safety have not been established in patients with HeFH or established ASCVD who require additional LDL-C lowering and it should not be used off-label for these indications at this time.

Clinical Safety:
Evinacumab was generally well tolerated and there were no differences in overall or mild adverse events between evinacumab and placebo. Antidrug antibodies did not develop during the treatment period in any of the patients in the primary 24-week efficacy trial. In the FDA pooled safety analysis, more serious adverse events were experienced by patients exposed to evinacumab compared to placebo (9.9% vs. 1.9%). There appears to be a dose-dependent relationship of serious adverse events with increasing evinacumab exposure. However, only one serious adverse event, anaphylactic reaction, was determined to be drug

related. In the pooled analysis, 3.4% of evinacumab patients discontinued the drug due to adverse events compared to 1.9% of placebo-treated patients. The most common adverse reactions that occurred more frequently than placebo is included in **Table 4**. Evinacumab is associated with hypersensitivity, including infusion reactions and anaphylaxis. Infusion reactions were reported in 6 (7%) of patients treated with evinacumab and 2(4%) of patients treated with placebo. There were no reports of rhabdomyolysis, significant creatine kinase (CK) elevations, or hepatic dysfunction. However, there is not enough safety data or sample size to detect low risk adverse events. Transient increases in blood pressure and heart rate during infusion were also observed. Based on nonclinical data, evinacumab is teratogenic and this is included as a warning and precaution in drug labeling.

Table 4: Adverse Reactions Occurring in >3% of Patients and Greater than Placebo[41]

Reactions	**Placebo (N = 54) %**	**Evinacumab (N = 81) %**
Nasopharyngitis	13%	16%
Influenza like illness	6%	7%
Dizziness	0%	6%
Rhinorrhea	0%	5%
Nausea	2%	5%

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Cardiovascular mortality
2) Non-fatal cardiovascular events
3) All-cause mortality
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Percent change in LDL-C from baseline to week 24

Table 5. Pharmacology and Pharmacokinetic Properties.[41]

Parameter	
Mechanism of Action	Evinacumab is a recombinant human monoclonal antibody that binds to and inhibits ANGPTl3, which is expressed in the liver and plays a role in the regulation of lipid metabolism by inhibiting lipoprotein lipase and endothelial lipase. Inhibition of ANGPTL3 leads to reduction in LDL-C, HDL-C and TG independent of the presence of LDL receptor by promoting VLDL processing and clearance upstream of LDL formation.
Oral Bioavailability	N/A: administered intravenously
Distribution and Protein Binding	4.8 L
Elimination	At higher concentrations, elimination is primarily through a non-saturable proteolytic pathway. At lower concentrations, eliminated through non-linear pathways.
Half-Life	Approximately 19 weeks
Metabolism	Not been characterized; expected to be degraded into small peptides and amino acids via catabolic pathways
Abbreviations: ANGPTL3: angiopoietin-like 3; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; TG: triglycerides; VLDL: very low density lipoprotein	

Table 6. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/N NH	Risk of Bias/ Applicability
1. ELIPSE HoFH[4] Part 1: DB, PC, PG, MC, RCT	1. Evinacumab (EVB) 15 mg/kg IV Q4W 2. Placebo 24 weeks	Demographics: 74% white Mean age 42 y/o 94% on statin 77% PCSK9 inhibitor 75% on ezetimibe Mean LDL 255 mg/dl 52% CVD Key Inclusion Criteria: ≥12 years of age with HoFH (genetic confirmation or clinical criteria) Key Exclusion Criteria: Tanner stage <2, LDL-C < 70 mg/dl, unstable background therapy, uncontrolled endocrine disease, unstable weight, HbA1c > 9%, recent CV event, NYHA class IV heart failure, SBP > 160 mm Hg, active malignancy, eGFR < 30 ml/min, AST/ALT > 3x ULN, CPK > 3 x ULN, TSH > 1.5x ULN, pregnant or breastfeeding, of childbearing potential unwilling to practice effective birth control	ITT: 1. 43 2. 22 PP: 1. 44 2. 21 Attrition: 1. 0 2. 0	Primary Endpoint: Percent change in LDL-C from baseline to week 24 1. -47.1% 2. + 1.9% LS mean difference -49%; 95% CI -65 to -33) P<0.001 Secondary Endpoints: Patients with ≥50% reduction from baseline in LDL-C 1. 24 (56%) 2. 1 (5%) OR 24.2; 95% CI 3.0-195.6 P=0.003	NA ARR 51%/ NNT 2	Discontinuations due to adverse events: 1. 0 2. 0 Serious adverse events: 1. 2 (5%) 2. 0 (0%)	NS NS	**Risk of Bias (low/high/unclear)**: Selection Bias: unclear; randomized using an interactive voice response system. More patients > 65 y/o in EVB arm versus placebo (19% vs. 0%), differences in baseline genotype and background therapy. Performance Bias: low; double-blinded, double dummy design. Potential unblinding due to hypersensitivity reactions but low incidence. Detection Bias: unclear; objective outcomes, but unclear if outcome assessors blinded Attrition Bias: low; efficacy analyses performed on ITT population; missing data imputed using mixed model repeated measured Reporting Bias: low; outcomes reported as prespecified Other Bias: unclear; Sponsored by Regeneron Pharmaceuticals who designed the trial protocol, selected participating sites. **Applicability**: Patient: Only 2 adolescent patients were included in the trial. Data cannot be generalized to high-risk CV populations who do not have HoFH. Intervention: Dose selection based on phase 2 data Comparator: placebo appropriate comparator with background lipid lowering therapy. Outcomes: Data on LDL-C only, which is a surrogate outcome. Study was not powered or designed to evaluate CV outcomes. Setting: multicenter study in 30 centers in 11 countries; majority outside of the U.S. (85%). 6 participating sites in the U.S. with 10 enrolled patients.

Abbreviations [alphabetical order]:ALT = alanine transaminase; AST = aspartate transaminase; ARR = absolute risk reduction; CI = confidence interval; CPK = creatine phosphokinase; CV = cardiovascular; CVD = cardiovascular disease; DB = double blind; eGFR = estimated glomerular filtration rate; HoFH = homozygous familial hypercholesterolemia; ITT = intention to treat; IV = intravenously; LDL-C = low density lipoprotein cholesterol; LS = least squares; mITT = modified intention to treat; N = number of subjects; MC = multicenter; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NYHA = new York heart association; OR = odds ratio; PC = placebo controlled; PCSK9 = proprotein convertase subtilsin-kexin type 9; PG = parallel group; PP = per protocol; RCT = randomized controlled trial; TSH = thyroid stimulating hormone; ULT = upper limit of normal; Q4W = every 4 weeks; y/o = years old.

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
cholestyramine (with sugar)	CHOLESTYRAMINE	ORAL	POWD PACK	Y
cholestyramine (with sugar)	QUESTRAN	ORAL	POWD PACK	Y
cholestyramine (with sugar)	CHOLESTYRAMINE	ORAL	POWDER	Y
cholestyramine (with sugar)	QUESTRAN	ORAL	POWDER	Y
cholestyramine/aspartame	CHOLESTYRAMINE LIGHT	ORAL	POWD PACK	Y
cholestyramine/aspartame	PREVALITE	ORAL	POWD PACK	Y
cholestyramine/aspartame	CHOLESTYRAMINE LIGHT	ORAL	POWDER	Y
cholestyramine/aspartame	PREVALITE	ORAL	POWDER	Y
cholestyramine/aspartame	QUESTRAN LIGHT	ORAL	POWDER	Y
evolocumab	REPATHA SURECLICK	SUB-Q	PEN INJCTR	Y
evolocumab	REPATHA SYRINGE	SUB-Q	SYRINGE	Y
evolocumab	REPATHA PUSHTRONEX	SUB-Q	WEAR INJCT	Y
ezetimibe	EZETIMIBE	ORAL	TABLET	Y
ezetimibe	ZETIA	ORAL	TABLET	Y
fenofibrate	FENOFIBRATE	ORAL	TABLET	Y
fenofibrate nanocrystallized	FENOFIBRATE	ORAL	TABLET	Y
fenofibrate nanocrystallized	TRICOR	ORAL	TABLET	Y
fenofibrate nanocrystallized	TRIGLIDE	ORAL	TABLET	Y
fenofibrate,micronized	ANTARA	ORAL	CAPSULE	Y
fenofibrate,micronized	FENOFIBRATE	ORAL	CAPSULE	Y
fenofibric acid (choline)	FENOFIBRIC ACID	ORAL	CAPSULE DR	Y
fenofibric acid (choline)	TRILIPIX	ORAL	CAPSULE DR	Y
omega-3 acid ethyl esters	LOVAZA	ORAL	CAPSULE	Y
omega-3 acid ethyl esters	OMEGA-3 ACID ETHYL ESTERS	ORAL	CAPSULE	Y
omega-3 acid ethyl esters	TRIKLO	ORAL	CAPSULE	Y
alirocumab	PRALUENT PEN	SUB-Q	PEN INJCTR	N
bempedoic acid	NEXLETOL	ORAL	TABLET	N
bempedoic acid/ezetimibe	NEXLIZET	ORAL	TABLET	N
colesevelam HCl	COLESEVELAM HCL	ORAL	POWD PACK	N
colesevelam HCl	WELCHOL	ORAL	POWD PACK	N

colesevelam HCl	COLESEVELAM HCL	ORAL	TABLET	N
colesevelam HCl	WELCHOL	ORAL	TABLET	N
colestipol HCl	COLESTID	ORAL	GRANULES	N
colestipol HCl	COLESTIPOL HCL	ORAL	GRANULES	N
colestipol HCl	COLESTID	ORAL	PACKET	N
colestipol HCl	COLESTIPOL HCL	ORAL	PACKET	N
colestipol HCl	COLESTID	ORAL	TABLET	N
colestipol HCl	COLESTIPOL HCL	ORAL	TABLET	N
fenofibrate	FENOFIBRATE	ORAL	CAPSULE	N
fenofibrate	LIPOFEN	ORAL	CAPSULE	N
fenofibrate	FENOFIBRATE	ORAL	TABLET	N
fenofibrate	FENOGLIDE	ORAL	TABLET	N
fenofibric acid	FENOFIBRIC ACID	ORAL	TABLET	N
fenofibric acid	FIBRICOR	ORAL	TABLET	N
gemfibrozil	GEMFIBROZIL	ORAL	TABLET	N
gemfibrozil	LOPID	ORAL	TABLET	N
icosapent ethyl	ICOSAPENT ETHYL	ORAL	CAPSULE	N
icosapent ethyl	VASCEPA	ORAL	CAPSULE	N
inositol	INOSITOL	ORAL	TABLET	N
lomitapide mesylate	JUXTAPID	ORAL	CAPSULE	N
niacin	NIACIN	ORAL	CAPSULE ER	N
niacin	NIACIN ER	ORAL	TAB ER 24H	N
niacin	NIASPAN	ORAL	TAB ER 24H	N
niacin	NIACIN	ORAL	TABLET	N
choline	CHOLINE	ORAL	TABLET	
niacin	NIACIN	ORAL	TABLET ER	
niacin	NIADELAY	ORAL	TABLET ER	
niacin (inositol niacinate)	NIACIN INOSITOL	ORAL	CAPSULE	
niacinamide	NIACINAMIDE	ORAL	TABLET	

Appendix 2: Abstracts of Comparative Clinical Trials

- Blom D, Harada-Shiba M, Rubba P, et al. Efficacy and Safety of Alirocumab in Adults with Homozygous Familial Hypercholesterolemia: The ODYSSEY HoFH Trial. J Am Coll Cardiol. 2020 Jul 14;76(2):131-142. doi: 10.1016/j.jacc.2020.05.027.

  Background: Homozygous familial hypercholesterolemia (HoFH) is characterized by extremely elevated low-density lipoprotein-cholesterol (LDL-C) levels and early onset atherosclerotic cardiovascular disease despite treatment with conventional lipid-lowering treatment.

  Objectives: This study was designed to assess LDL-C reduction with the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab in adult patients with HoFH.

  Methods: This randomized, double-blind, placebo-controlled, parallel-group, phase 3 study evaluated efficacy and safety of alirocumab 150 mg every 2 weeks. The primary endpoint was percent reduction from baseline in LDL-C versus placebo after 12 weeks of treatment.

  Results: Patients (N = 69) were randomized 2:1 to alirocumab or placebo. At baseline, background lipid-lowering treatment included 67 patients receiving statin (59 patients on high-intensity statin); 50 patients on ezetimibe; 10 patients on lomitapide; and 10 patients undergoing apheresis. Mean baseline LDL-C was 259.6 mg/dl in the placebo group and 295.0 mg/dl in the alirocumab group. At week 12, the least squares mean difference in LDL-C percent change from baseline was -35.6% (alirocumab [-26.9%] vs. placebo [8.6%]; $p < 0.0001$). Reductions (least squares mean difference) in other atherogenic lipids at week 12 were: apolipoprotein B, -29.8%; non-high-density lipoprotein cholesterol, -32.9%; total cholesterol, -26.5%; and lipoprotein(a), -28.4% (all $p < 0.0001$). No serious adverse events, permanent treatment discontinuations, or deaths due to treatment-emergent adverse events were reported during the double-blind treatment period.

  Conclusions: In the largest randomized controlled interventional trial in HoFH patients to date, alirocumab resulted in significant and clinically meaningful reductions in LDL-C at week 12. Alirocumab was generally well tolerated, with a safety profile comparable to that of placebo. (Study in Participants With Homozygous Familial Hypercholesterolemia [HoFH] [ODYSSEY HoFH] NCT03156621.).

- Schwartz G, Steg P, Szarek M, et al. Peripheral Artery Disease and Venous Thromboembolic Events After Acute Coronary Syndrome: Role of Lipoprotein(a) and Modification by Alirocumab: Prespecified Analysis of the ODYSSEY OUTCOMES Randomized Clinical Trial. 2020 May 19;141(20):1608-1617. doi: 10.1161/CIRCULATIONAHA.120.046524. Epub 2020 Mar 29.

  Background: Patients with acute coronary syndrome are at risk for peripheral artery disease (PAD) events and venous thromboembolism (VTE). PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors reduce lipoprotein(a) and low-density lipoprotein cholesterol (LDL-C) levels. Our objective was to ascertain whether PCSK9 inhibition reduces the risk of PAD events or VTE after acute coronary syndrome, and if such effects are related to levels of lipoprotein(a) or LDL-C.

  Methods: This was a prespecified analysis of the ODYSSEY OUTCOMES randomized clinical trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome), which was conducted in 18 924 patients with recent acute coronary syndrome on intensive or maximum-tolerated statin treatment who were randomized to the PCSK9 inhibitor alirocumab or placebo. In a prespecified analysis, PAD events (critical limb ischemia, limb revascularization, or

amputation for ischemia) and VTE (deep vein thrombosis or pulmonary embolism) were assessed. LDL-C was corrected (LDL-Ccorrected) for cholesterol content in lipoprotein(a).

Results: At baseline, median lipoprotein(a) and LDL-Ccorrected were 21 and 75 mg/dL, respectively; with alirocumab, median relative reductions were 23.5% and 70.6%, respectively. PAD events and VTE occurred in 246 and 92 patients, respectively. In the placebo group, risk of PAD events was related to baseline quartile of lipoprotein(a) (Ptrend=0.0021), and tended to associate with baseline quartile of LDL-Ccorrected (Ptrend=0.06); VTE tended to associate with baseline quartile of lipoprotein(a) (Ptrend=0.06), but not LDL-Ccorrected (Ptrend=0.85). Alirocumab reduced risk of PAD events (hazard ratio [HR], 0.69 [95% CI, 0.54-0.89]; P=0.004), with nonsignificantly fewer VTE events (HR, 0.67 [95% CI, 0.44-1.01]; P=0.06). Reduction in PAD events with alirocumab was associated with baseline quartile of lipoprotein(a) (Ptrend=0.03), but not LDL-Ccorrected (Ptrend=0.50). With alirocumab, the change from baseline to Month 4 in lipoprotein(a), but not LDL-Ccorrected, was associated with the risk of VTE and the composite of VTE and PAD events.

Conclusions: In statin-treated patients with recent acute coronary syndrome, risk of PAD events is related to lipoprotein(a) level and is reduced by alirocumab, particularly among those with high lipoprotein(a). Further study is required to confirm whether risk of VTE is related to lipoprotein(a) level and its reduction with alirocumab. Registration: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01663402.

- Nicholls S, LIncoff M, Garia M, et al. Effect of High-Dose Omega-3 Fatty Acids vs Corn Oil on Major Adverse Cardiovascular Events in Patients at High Cardiovascular Risk: The STRENGTH Randomized Clinical Trial. 2020 Dec 8;324(22):2268-2280. doi: 10.1001/jama.2020.22258.

  Objective: To determine the effects on cardiovascular outcomes of a carboxylic acid formulation of EPA and DHA (omega-3 CA) with documented favorable effects on lipid and inflammatory markers in patients with atherogenic dyslipidemia and high cardiovascular risk.

  Design, setting, and participants: A double-blind, randomized, multicenter trial (enrollment October 30, 2014, to June 14, 2017; study termination January 8, 2020; last patient visit May 14, 2020) comparing omega-3 CA with corn oil in statin-treated participants with high cardiovascular risk, hypertriglyceridemia, and low levels of high-density lipoprotein cholesterol (HDL-C). A total of 13 078 patients were randomized at 675 academic and community hospitals in 22 countries in North America, Europe, South America, Asia, Australia, New Zealand, and South Africa.

  Interventions: Participants were randomized to receive 4 g/d of omega-3 CA (n = 6539) or corn oil, which was intended to serve as an inert comparator (n = 6539), in addition to usual background therapies, including statins.

  Main outcomes and measures: The primary efficacy measure was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina requiring hospitalization.

  Results: When 1384 patients had experienced a primary end point event (of a planned 1600 events), the trial was prematurely halted based on an interim analysis that indicated a low probability of clinical benefit of omega-3 CA vs the corn oil comparator. Among the 13 078 treated patients (mean [SD] age, 62.5 [9.0] years; 35% women; 70% with diabetes; median low-density lipoprotein [LDL] cholesterol level, 75.0 mg/dL; median triglycerides level, 240 mg/dL; median HDL-C level, 36 mg/dL; and median high-sensitivity C-reactive protein level, 2.1 mg/L), 12 633 (96.6%) completed the trial with ascertainment of primary end point status. The primary end point occurred in 785 patients (12.0%) treated with omega-3 CA vs 795 (12.2%) treated with corn oil (hazard ratio,

0.99 [95% CI, 0.90-1.09]; P = .84). A greater rate of gastrointestinal adverse events was observed in the omega-3 CA group (24.7%) compared with corn oil-treated patients (14.7%).

Conclusions and relevance: Among statin-treated patients at high cardiovascular risk, the addition of omega-3 CA, compared with corn oil, to usual background therapies resulted in no significant difference in a composite outcome of major adverse cardiovascular events. These findings do not support use of this omega-3 fatty acid formulation to reduce major adverse cardiovascular events in high-risk patients.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) ALL <1946 to June 11, 2021>

1 ezetimibe.mp. or Ezetimibe/ 3797
2 bile acid sequestrants.mp. 472
3 colestipol.mp. or Colestipol/ 546
4 cholestyramine.mp. or Cholestyramine Resin/ 3548
5 colesevelam.mp. or Colesevelam Hydrochloride/ 318
6 alirocumab.mp. 735
7 evolocumab.mp. 799
8 PCSK9 inhibitors.mp. 1052
9 fenofibrate.mp. or Fenofibrate/ 3932
10 gemfibrozil.mp. or Gemfibrozil/ 2222
11 icosapent ethyl.mp. 206
12 omega-3 fatty acids.mp. or Fatty Acids, Omega-3/ 17791
13 niacin.mp. or Niacin/ 13716
14 bempedoic acid.mp. 132
15 evinacumab.mp. 56
16 nonstatin.mp. 324
17 cardiovascular disease.mp. or Cardiovascular Diseases/ 246719
18 atherosclerotic cardiovascular disease.mp. 4366
19 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 45776
20 17 or 18 246719
21 19 and 20 4490
22 limit 21 to (english language and humans and yr="2020 -Current" and (clinical trial, all or meta analysis or randomized controlled trial or "systematic review")) 71
23 from 22 keep 2-5,7,11,16,18,20,23-25,36,40-42,44,46,49,52-54,56 23

Appendix 4: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

EVKEEZA™ (evinacumab-dgnb) injection, for intravenous use

Initial U.S. Approval: 2021

INDICATIONS AND USAGE

EVKEEZA is an ANGPTL3 (angiopoietin-like 3) inhibitor indicated as an adjunct to other low-density lipoprotein-cholesterol (LDL-C) lowering therapies for the treatment of adult and pediatric patients, aged 12 years and older, with homozygous familial hypercholesterolemia (HoFH). (1)

Limitations of Use:

- The safety and effectiveness of EVKEEZA have not been established in patients with other causes of hypercholesterolemia, including those with heterozygous familial hypercholesterolemia (HeFH). (1)
- The effects of EVKEEZA on cardiovascular morbidity and mortality have not been determined. (1)

DOSAGE AND ADMINISTRATION

- The recommended dose of EVKEEZA is 15 mg/kg administered by intravenous (IV) infusion once monthly (every 4 weeks). (2.1)
- See the Full Prescribing Information for preparation instructions for the intravenous infusion. (2.2)
- Administer the diluted solution via IV infusion over 60 minutes through an IV line containing a sterile, in-line or add-on, 0.2 micron to 5 micron filter. (2.3)
- Do not mix other medications with EVKEEZA or administer other medications concomitantly via the same infusion line. (2.3)
- The rate of infusion may be slowed, interrupted or discontinued if the patient develops any signs of adverse reactions, including infusion or hypersensitivity reactions. (2.3).

DOSAGE FORMS AND STRENGTHS

- Injection: 345 mg/2.3 mL (150 mg/mL) and 1,200 mg/8 mL (150 mg/mL) solution in single-dose vials. (3)

CONTRAINDICATIONS

- History of serious hypersensitivity reactions to evinacumab-dgnb or to any of the excipients in EVKEEZA. (4)

WARNINGS AND PRECAUTIONS

- *Serious Hypersensitivity Reactions*: Have occurred with EVKEEZA in clinical trials. If a serious hypersensitivity reaction occurs, discontinue EVKEEZA, treat according to standard-of-care and monitor until signs and symptoms resolve. (5.1)
- *Embryo-Fetal Toxicity*: EVKEEZA may cause fetal harm based on animal studies. Advise patients who may become pregnant of the risk to a fetus. Consider obtaining a pregnancy test prior to initiating treatment with EVKEEZA. Advise patients who may become pregnant to use contraception during treatment and for at least 5 months following the last dose. (5.2, 8.1, 8.3)

ADVERSE REACTIONS

Common adverse reactions (≥ 5%) were nasopharyngitis, influenza-like illness, dizziness, rhinorrhea, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Regeneron at 1-833-385-3392 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Revised: 02/2021

Appendix 5: Key Inclusion Criteria

Population	**Individuals with cardiovascular disease or high-risk cardiovascular disease**
Intervention	Non-statin lipid lowering therapy
Comparator	Placebo or active control
Outcomes	Cardiovascular events, all-cause mortality, cardiovascular mortality
Timing	At least 12 weeks
Setting	Outpatient or inpatient after acute coronary syndrome

Evinacumab

Goal(s):

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

Length of Authorization:

- Up to 12 months

Requires PA:

- Evinacumab (Evkeeza™) – pharmacy and provider administered claims

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code; go to #2	
2. Is the patient 12 years or older with a diagnosis of homozygous or familial hypercholesterolemia (HoFH) diagnosed by genetic testing or the following clinical criteria? • Untreated LDL-C > 500 mg/dl or treated LDL-C > 300 mg/dl	**Yes:** Go to #3	**No:** Pass to RPh; deny for medical appropriateness
3. Does the patient still have an LDL-C of ≥ 100 mg/dl while taking a maximally tolerated statin and ezetimibe and/or a PCSK9 inhibitor (alirocumab or evolocumab)?	**Yes:** Go to #4 Recent LDL-C _____ mg/dL Date:_____	**No:** Pass to RPh; deny for medical appropriateness.
4. Is the patient of childbearing potential?	**Yes:** Go to #5	**No:** Approve for up to 12 months

Approval Criteria		
5. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh; deny for medical appropriateness.	**No:** Go to #6
6. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh; deny for medical appropriateness.

P&T / DUR Review: *08/21 (MH)*
Implementation:

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 an 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: *8/20 (MH); 5/19; 1/18; 11/16; 11/15*
Implementation: *7/1/2019; 3/1/18; 1/1/1*

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	
7. What diagnosis is being treated?	Record ICD10 code; go to #2

Approval Criteria		
8. 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 (MH)*
Implementation: *9/1/20*

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:

- 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

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: Overactive Bladder Drugs

Date of Review: August 2021

Date of Last Review: September 2018
Dates of Literature Search: 07/01/2018 - 04/21/2021
Brand Name (Manufacturer): Gemtesa® (Urovant Sciences, Inc.)
Dossier Received: yes

Generic Name: vibegron

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

Purpose for Class Update:
The purpose of this update is to identify and evaluate new evidence related to the treatment of overactive bladder (OAB) and determine the place in therapy for a newly approved OAB treatment.

Research Questions:
1. Is there any new high-quality comparative evidence on the efficacy and harms of therapies used for OAB?
2. Is there evidence regarding subgroups of patients based on demographics (age, racial groups, gender), socioeconomic status, other medications (drug-drug interactions), comorbidities (drug-disease interactions), for which a specific OAB therapy is more effective or associated with fewer harms?
3. What is the efficacy and safety of vibegron for the treatment of OAB?

Conclusions:
- There were 2 systematic reviews, 2 new guidelines, 1 new drug and 1 new formulation and 1 new indication identified since the last review. No new compelling evidence suggests clinically significant differences in efficacy between the pharmacotherapies for OAB. Anticholinergic treatments were consistently associated with a higher incidence of dry mouth.
- An Agency for Healthcare Research and Quality (AHRQ) evaluated nonsurgical treatment of urinary incontinence in women and found pharmacotherapy (e.g., antimuscarinics or beta-3 adrenergic agonists) to be effective for symptom management of OAB but when used alone were less effective than behavioral therapy.[1] There were no clinically relevant differences in efficacy between pharmacotherapies; however, anticholinergics were more commonly associated with dry mouth. In women 60 years and older with stress or urgency urinary incontinence (UUI), moderate quality evidence found anticholinergics to be more effective in improving symptoms than hormone therapy (OR 5.53; 95% CI, 1.03 to 29.56).[1]
- A good quality systematic review on the treatment of OAB in adults found small, but unlikely to be clinically impactful differences, between monotherapy treatments for OAB and monotherapy compared to combination treatments.[2] Changes in key outcomes (e.g., incontinence, urgency, and micturitions)

Author: Kathy Sentena, PharmD

demonstrated absolute differences of less than half of an episode per day. Dry mouth was more often associated with antimuscarinics compared to mirabegron.[2]

- Guidance from the National Institute for Health and Care Excellence (NICE) and American Urology Association (AUA)/Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) supports current Oregon Health Authority (OHA) policy.
- A new beta-3 adrenergic agonist, vibegron, was approved for the use in adult patients with OAB. Improvements in daily micturitions were demonstrated in 2 phase 3 trials with daily reductions of -1.8 episodes with the vibegron 75 mg dose compared to -1.3 episodes for placebo (least square mean difference [LSMD] -0.5; 95% CI, -0.8 to -0.2; P<0.001).[3] Overall efficacy is modest and not clinically impactful for most patients.
- Common adverse events experienced with vibegron included headache, diarrhea, nausea and upper respiratory infection. Severe adverse events were rare and similar to placebo.[3]

Recommendations:

- Continue vibegron designation as non-preferred on the preferred drug list (PDL).
- No changes to the PDL are warranted based on the evidence identified since the last review.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy

- This class was previously reviewed in September of 2018. No clinically significant efficacy or serious safety differences were found between therapies for OAB based on the findings of a Drug Effectiveness Review Project (DERP) report. Analysis of efficacy and costs resulted in no changes to the PDL.
- Oxybutynin and fesoterodine are preferred products on the PDL. Non-preferred products are subject to the general non-preferred drug prior authorization (PA) criteria. Almost 90% of the utilization in this class is for preferred products and the overall spend is not a significant contributor to OHA drug costs in the Fee-For-Service population.

Background:

OAB is a common condition with the highest prevalence in geriatric patients, affecting approximately 33% of those 75 years and older.[4] Guidelines define OAB as the presence of urinary urgency, often associated with frequency and nocturia, with or without UUI and without urinary tract infection or other pathology.[5,6] Urgency is the most common patient reported symptom of OAB and the most troubling symptom is incontinence, often reducing the quality of life in those affected. OAB related to incontinence is often referred to as “OAB wet” and patients without incontinence is referred to “OAB dry”.[4] There are three types of urinary incontinence classifications: OAB with urgency incontinence (OAB wet); stress urinary incontinence; and mixed urinary incontinence with components of both OAB wet and stress urinary incontinence.[4] Stress incontinence is associated with involuntary urine loss on effort or physical exertion. Urinary symptoms can also arise from neurological conditions in the brain, spinal cord and peripheral nervous system.

Treatment of OAB includes non-pharmacological as well as pharmacological therapies. First-line recommendations are weight-loss, pelvic floor training, and biofeedback.[5] Behavioral therapy is very effective in patients with OAB and is often considered more effective by patients than pharmacological therapies. The combination of behavioral and pharmacological treatment has been shown to be more effective than placebo.[7] The use of pharmacologic treatments in OAB is limited by modest efficacy and poor tolerability due to adverse events. If drug treatment is warranted, guidelines recommend antimuscarinics (e.g., tolterodine, oxybutynin, solifenacin and darifenacin) or beta-3 adrenergic agonists (e.g., mirabegron) based on moderate evidence of efficacy.[5] There are no approved therapies for stress urinary incontinence; however, duloxetine is used off-label.[7]

Antimuscarinic therapies are recommended as first-line pharmacotherapy due to efficacy and cost.[7] A recent review by the AHRQ evaluated urinary incontinence in women and reported evidence that anticholinergics were more effective in cure, improvement and patient satisfaction compared to placebo based on high quality of evidence.[7] For the treatment of mixed urinary incontinence, duloxetine and tolterodine had evidence for efficacy in reductions in episodes based on low quality data. Other sources have found no difference in efficacy between antimuscarinic therapies for urinary incontinence.[8] Adverse events associated with antimuscarinics include: dry mouth, constipation, and dry/itchy eyes. Long-term use of antimuscarinics have been reported to possibly increase the risks of cognitive impairment and dementia.[4]

Beta-3 adrenergic agonists are a new class of therapies used for the treatment of OAB. Mirabegron was the first agent in the class approved by the Food and Drug Administration (FDA).[9] Evidence has demonstrated similar efficacy to antimuscarinics. Common adverse events associated with mirabegron use in clinical studies were hypertension, nasopharyngitis, urinary tract infection and headache. Mirabegron is not recommended for patients with severe uncontrolled hypertension (greater or equal to 180 mmHg/ 110 mmHg) due to dose related increases in supine blood pressure with a mean maximum increase of approximately 3.5 mmHg systolic and 1.5 mmHg diastolic greater than placebo.[10] Postmarketing data has demonstrated urinary retention in patients with bladder outlet obstruction (BOO) and in patients on antimuscarinic medications. Caution is advised if administering mirabegron to these patient populations.

Combination therapy with antimuscarinics and beta-3 adrenergic agonists can be used in patients refractory to monotherapy.[5] Studies evaluating mirabegron (25 mg and 50 mg) in combination with solifenacin 5 mg were found to be more effective than monotherapy by a difference in daily reductions in urinary incontinence episodes of -0.20 to -0.27, which are unlikely to be clinically significant.[11,12] Botulism toxin injections are an alternative therapy in patients with proven detrusor overactivity when less invasive therapies fail to control symptoms, but are associated with an increased risk of urinary tract infections and urinary dysfunction.[7] Surgical therapies can be offered as a third-line intervention.

Outcomes used to evaluate the efficacy of treatment in OAB are mostly subjective and associated with a high placebo response rate. Improvement or cure of UUI and number of daily micturitions are commonly used outcomes. A clinically meaningful response to patients is a reduction in UUI of 90% or more.[4] Clinical trials commonly use voiding diaries to measure urinary frequency by tracking micturitions (with around 7 micturitions a day considered normal), nocturia (waking due to the need to void) and UUI (involuntary leakage of urine associated with sudden need to void). The “need to urinate immediately” is an outcome used in the vibegron trials that has not been previously used for approval of other OAB agents. Quality of life, as measured by validated scales such as the Overactive Bladder Questionnaire (OAB-q) and Patient Global Impression Scale (PGI) are appropriate for assessing treatment effect on patient well-being. The OAB-q is separated into two sections: a validated 8-item symptom bother scale (SS) (score ranges from 0-100 in which higher scores indicate worse symptoms) and 25-item health-related quality of life (HRQL) scale rating subscales (e.g., coping, sleep, concern and social interaction)(score ranges 0-100 with high scores indicating improved quality of life).[13] The minimum important difference (MID) for the SS ranges from -13 to -25 and +5 to +12 for the HRQL.[14] The PGI is a reliable indicator of disease severity on activities of daily living and psychological well-being. Lower scores indicated improved quality of life.[15]

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:

AHRQ – Nonsurgical Treatments for Urinary Incontinence in Women

A systematic review and meta-analysis was done by AHRQ in 2018 to update findings from a 2012 report on the diagnosis and treatment of urinary incontinence in women.[1] Both stress and urgency incontinence were included. A systematic literature search of adult women with urinary incontinence was conducted from January 1, 2011 thru December 4, 2017 which identified 233 studies for inclusion. Evidence on non-pharmacological and pharmacological therapies was included. Pharmacological interventions included anticholinergics, onabotulinum toxin A, hormones (estrogen), alpha agonists, beta-3 agonists (no efficacy outcomes available for inclusion), antidepressants and periurethral bulking agents. The median age was 55 years old and median trial size was 85 participants.[1] Thirty-three trials were identified for stress incontinence, 16 for urgency incontinence and 4 with mixed stress/urgency incontinence. The primary outcome was the improvement and cure of urinary incontinence, as well as satisfaction with the treatment outcome and quality of life.

Stress incontinence is primarily treated with hormones or alpha agonists. Urgency incontinence treatments studied included tolterodine, oxybutynin, mirabegron, darifenacin, fesoterodine, flavoxate, phenylpropanolamine, pilocarpine, propantheline, and solifenacin. A network meta-analysis was used to combine results of study findings for urinary incontinence. Behavioral therapy was found to be effective in patients with stress incontinence compared to no therapy (OR 3.1; 95% CI, 2.2 to 4.4) and similar findings when used in combination with alpha agonists or hormones (OR 4.4; 95% CI, 1.4 to 13.8; moderate strength of evidence).[1]

There were 33 studies that informed findings for urgency incontinence. High quality evidence found behavioral therapy to be more effective for cure compared to no treatment or placebo (OR 2.75; 95% CI, 1.53 to 4.92).[1] Anticholinergics were also more effective than no treatment or placebo on cure rates based on high quality evidence (OR 1.80; 95% CI, 1.29 to 2.52). High quality of evidence demonstrated behavioral therapy to not be more effective to achieve cure compared to anticholinergics (OR 1.53; 95% CI, 0.90 to 2.60).[1] There were no direct comparisons of the combination of behavioral therapy and anticholinergics to no treatment or placebo.

In women who were 60 years and older with stress or UUI, moderate quality evidence found combination of behavioral therapy with hormones or neuromodulation was more likely to achieve cure compared to no treatment. Cure rates were higher in this population for behavioral therapy compared to anticholinergics (OR 2.76; 95% CI, 1.09 to 6.99) (moderate strength of evidence).[1]

Sixty-four studies provided evidence for the interventions to improve UUI. Behavioral therapy, anticholinergics and the combination of the two were more effective than no treatment based on high-quality evidence. Behavioral therapy was more likely to achieve improvement in UUI compared to anticholinergics (OR 4.2; 95% CI, 1.6 to 10.9) (high strength of evidence).[1]

In older women (60 years and older) with stress or UUI, anticholinergics were more likely to have symptom improvement than those patients who used hormone therapy (OR 5.53; 95% CI, 1.03 to 29.56) based on moderate quality evidence.[1]

In women with UUI, patient satisfaction was higher with behavioral therapy compared to anticholinergics (OR 8.2; 95% CI, 1.7 to 39.4) based on high quality of evidence. There is moderate quality of evidence that compared to no treatment, anticholinergics alone were more effective in achieving satisfaction (OR 2.6; 95% CI, 2.1 to 3.3).[1] In older women, behavioral therapy and anticholinergics were more effective in controlling UI symptoms compared to no treatment based on moderate evidence.

There was high quality evidence that dry mouth was the most common adverse event associated with the use of anticholinergics.[1]

Hsu, et al – Updating the Evidence on Drugs to Treat Overactive Bladder

A high quality systematic review and meta-analysis looked at the evidence for the treatment of OAB.[2] The original review was conducted in consultation with the Drug Effectiveness Review Project (DERP) with an updated search following the same process. The evidence was searched from 2012 to September 2018 which identified 51 studies. Evidence was included for adult patients with OAB with UUI and mixed incontinence. Exclusion criteria included patients with stress incontinence or neurogenic detrusor overactivity. Drugs included in the search were the following: darifenacin, fesoterodine, mirabegron, oxybutynin, solifenacin, tolterodine, and trospium. Twenty of the studies were new since the original DERP report. Five were good quality, 10 were fair quality and 5 were poor quality due to unclear allocation concealment, blinding and missing data. A majority of participants were female (77%), 59.2% had previous pharmacotherapy for OAB and the average duration of OAB symptoms was 67.4 months.[2] The outcomes of interest were: incontinence episodes in 24 hours, 3-days with no incontinence, urgency episodes in 24 hours, and micturitions in 24 hours.

Results for the findings of the meta-analysis are reported in **Table 1**. Only statistically significant findings are listed. There were no significant differences for any outcomes between mirabegron 50 mg and tolterodine ER 4 mg based on 3 studies. Solifenacin was compared to oxybutynin which demonstrated no difference for the outcomes of urgency episodes in 24 hours and micturitions in 24 hours. Combination therapy with mirabegron and solifenacin was more effective for all outcomes compared to solifenacin alone; however, the differences were small and unlikely to be clinically impactful. Both groups were found to have clinically meaningful changes in OAB-q Symptom Bother score. The combination was also more effective than mirabegron alone except for the outcome of no incontinence over 3 days. Comparisons between mirabegron and solifenacin found solifenacin to be more effective at reducing incontinence and micturitions. Mirabegron and solifenacin were both found to achieve minimal clinically important differences (MCID) for the OAB-q Symptom Bother score and solifenacin had significantly better scores than mirabegron. Dry mouth was consistently more common with solifenacin compared to mirabegron throughout all the studies. Overall, the evidence suggests minimal clinical difference in efficacy between monotherapy comparisons and combination treatment compared to monotherapy for the treatment of symptoms of OAB.

Table 1. Results for Efficacy Outcomes for the use of Treatments in OAB[2]

Comparison	Outcome	Result*
Mirabegron 50 mg + Solifenacin 5 mg Vs. Solifenacin 5 mg	Incontinence episodes in 24 hours	-0.18 (95% CI, -0.31 to -0.05)
	3-day 0 incontinence	RR 1.23 (95% CI, 1.13 to 1.34)
	Urgency episodes in 24 hours	-0.58 (95% CI, -0.89 to -0.28)
	Micturitions in 24 hours	-0.41 (95% CI, -0.54 to -0.27)
Mirabegron 50 mg + Solifenacin 5 mg	Incontinence episodes in 24 hours	-0.34 (95% CI, -0.52 to -0.16)

Vs. Mirabegron 50 mg	Urgency episodes in 24 hours	-0.77 (95% CI, -1.02 to -0.52)
	Micturitions in 24 hours	-0.56 (95% CI, -0.75 to -0.37)
Mirabegron 50 mg Vs. Solifenacin 5 mg	Incontinence episodes in 24 hours	+0.20 (95% CI, 0.02 to 0.38)
	Micturition in 24 hours	+0.18 (95% CI, 0.01 to 0.35)
Fesoterodine 8 mg Vs. Tolterodine 4 mg	Incontinence episodes per 24 hours	-0.18 (-0.29 to -0.07)
	3-day 0 incontinence	RR 1.10 (95% CI, 1.04 to 1.16)
	Urgency episodes in 24 hours	-0.40 (95% CI, -0.69 to -0.12)
	Micturitions per 24 hours	-0.22 (95% CI, -0.43 to -0.01)
Solifenacin 5 mg Vs. Tolterodine 4 mg	Incontinence episodes in 24 hours	-0.36 (95% CI, -0.58 to -0.13)
	Urgency episodes in 24 hours	-0.49 (95% CI, -0.79 to -0.20)
Tolterodine Vs. Oxybutynin	3-day 0 incontinence	RR 0.73 (95% CI, 0.55 to 0.97)
Key: * All results statistically significant		
Abbreviations: RR = relative risk		

After review, 9 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).[16–24]

New Guidelines:
High Quality Guidelines:

<u>NICE – Urinary Incontinence and Pelvic Organ Prolapse in Women</u>
A 2019 guideline on the management of women with urinary incontinence and pelvic organ prolapse was produced by NICE.[25] First-line recommendations were for the use of bladder training for at least 6 weeks for women who have urgency or mixed urinary incontinence. Combination therapy of OAB medication with bladder training should be considered if frequency is a bothersome symptom and there is not satisfactory benefit from bladder training programs alone. If medication is being considered, the patient should be counseled on expected efficacy, common adverse events, and the need for up to 4 weeks of therapy to see substantial benefit and anticholinergic use long-term may affect cognitive function. The anticholinergic with the lowest acquisition cost should be recommended to women with OAB or mixed urinary incontinence in women. An alternative medication can be offered to women who do not experience relief with the first medication, after at least 4 weeks of therapy. Offer transdermal OAB treatment to women who are unable to tolerate oral medications. Mirabegron is recommended for patients with OAB in which antimuscarinic drugs are contraindicated, clinically ineffective or have unacceptable adverse reactions.[26] It is not recommended to use flavoxate, propantheline, or imipramine for OAB or urinary incontinence. Oxybutynin (immediate release) should not be recommended to older women who may be at risk of sudden deterioration in their physical or mental health. The use of desmopressin may be considered for patients with OAB and urinary incontinence who have nocturia; however, use with caution in patients with cystic fibrosis and in those 65 years or older with

cardiovascular (CV) disease or hypertension. In women with stress urinary incontinence, the use of duloxetine is not recommended first-line and should be used second-line in women who prefer pharmacological therapy to surgical treatment. The use of systemic hormone treatment is not recommended; however, intravaginal estrogens can be offered to treat OAB in postmenopausal women with vaginal atrophy. Women 75 years and older should have OAB medications reviewed every 6 months and all other women should be evaluated annually.

AUA/SUFU – Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) In Adults

In 2019 AUA/SUFU updated their guidance on the treatment of OAB in adults.[5] The systematic review and data extraction was done as part of the AHRQ Evidence Report/Technology Assessment. Conflicts of interest with industry were present for all authors. The publication was extensively peer reviewed. The guideline focus was for diagnosis and management of OAB with literature current through October 2018. An amendment followed the initial guidance to include recommendations on the use of combination therapy in patients with OAB.[6] Individual quality studies were graded according to Evidence-based practice center and the body of evidence was assigned a strength rating of A (high), B (moderate) or C (low). Insufficient evidence on additional treatment information was designated as a Clinical Principle or Expert Opinion.[5]

Pharmacotherapy recommendations for patients with OAB are outlined in **Table 2**. Dose modification or use of a different antimuscarinic or beta-3 adrenergic agonist is recommended for patients who have inadequate symptom control or adverse reactions to initial therapy. Antimuscarinics should not be used in patients with narrow-angle glaucoma unless approved by an ophthalmologist. Patients who have impaired gastric emptying or history of urinary retention should be very cautious about using antimuscarinics. Antimuscarinics should be used cautiously in patients if already taking therapies with anticholinergic properties. Both antimuscarinics and beta-3 adrenergic agonists should be used with caution in patients that are frail with OAB.

Table 2. AUA/SUFU Treatment Recommendations for Overactive Bladder[5,6]

Recommendation	Grade
First-Line	
Behavioral therapies (e.g., bladder training, control strategies, pelvic floor muscle training, fluid management	B
Behavioral therapies may be combined with pharmacological therapies	C
Second-line	
Oral antimuscarinics or beta-3 adrenergic agonist are recommended	B
ER formulations should be used, if available, over IR due to a lower incidence of dry mouth	B
Transdermal oxybutynin (patch or gel) can be offered	C
Combination therapy with an antimuscarinic and beta-3 adrenergic agonist can be considered for patients refractory to monotherapy with either antimuscarinics or beta-3 adrenergic agonist	B
Abbreviations: ER – extended release; IR – immediate release	

After review, 2 guidelines were excluded due to poor quality.[27,28]

New Formulations or Indications:

Mirabegron (Myrbetriq) –Received FDA-approval for 2 new indications since the last review.

1) In March of 2021 mirabegron received FDA approval for use in pediatric patients 3 years and older, weighing 35 kg or more, with neurogenic detrusor overactivity (NDO).[10] Mirabegron tablets and mirabegron granules (used in oral suspension) are not interchangeable and should not be combined. For pediatric patients weighing less than 35 kg, mirabegron granules should be used (recommendations from prescribing material despite approval for patients 35 kg or more). For pediatric patients weighting more than 35 kg the recommended starting dose is for mirabegron 25 mg orally once daily. After 4 to 8 weeks the dose can be increased to 50 mg daily. The recommended starting dose of mirabegron granules is 6 ml (48 mg) of the extended-release oral suspension orally once daily. After 4 to 8 weeks the dose can be increased to 10 ml (80 mg) once daily.

Mirabegron granules were studied in a 52-week, open-label trial in 86 pediatric patients (ages 3-17 years) with NDO and involuntary detrusor contractions with detrusor pressure increase greater than 15 cm H_2O and patients or caregivers practiced clean intermittent catheterization (CIC).[10] The primary endpoint was change from baseline in patients' maximum cystometric (bladder) capacity (MCC) measured at 24 weeks. Patients were stratified by age: 3 years to less than 12 years (n=43) and 12 years to 17 years (n=25). The MCC was increased 72 ml (95% CI, 45 to 99) in patients 3-12 years and 113 ml (95% CI, 79 to 147) in patients 12-17 years.[10]

2) In 2018 mirabegron was approved for use in combination with solifenacin succinate for adult patients with OAB with symptoms of urge urinary incontinence, urgency, and urinary frequency.[10] Two, 12-week double-blind, randomized controlled trials provided evidence for approval. Combination therapy was found to reduce incontinence episodes by -0.25 (95% CI, -0.49 to -0.01) to -0.20 (95% CI, -0.44 to 0.04) compared to solifenacin monotherapy. Differences from mirabegron monotherapy ranged from -0.34 (95% CI, -0.58 to -0.10) to -0.23 (95% CI, -0.47 to 0.01).[10] Overall differences were small and unlikely to be clinically impactful.

Solifenacin (Vesicare LS) – solifenacin is an oral suspension approved in May of 2020 for the treatment of neurogenic detrusor overactivity (NDO) in pediatric patients 2 years and older.[29] Solifenacin LS dosing is weight based with the oral suspension available as a 1 mg/mL solution. Approval was based off of 2 small, 52-week, open-label studies which included a total of 95 patients. The primary endpoint was change in patients' maximum cystometric (bladder) capacity (MCC) after 24 weeks. An increase of 39-57 mLs was demonstrated with solifenacin LS in patients 2 to 17 years.[29]

New FDA Safety Alerts:

No safety alerts identified.

Randomized Controlled Trials:
A total of 41 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION: Vibegron (Gemtesa®)

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:
Vibegron (Gemtesa®) is FDA approved for the treatment of overactive bladder (OAB) with symptoms of urinary incontinence, urgency, and urinary frequency.[30] Vibegron is the second beta-3 adrenergic receptor agonist approved for use in OAB.[30] Vibegron selectively stimulates the beta-3 adrenergic receptor in the bladder to increase bladder capacity by relaxing the detrusor smooth muscle during bladder filling.

Summary of Clinical Efficacy:
Vibegron is the second beta-3 adrenergic receptor agonist approved for use in OAB.[30] Vibegron selectively stimulates the beta-3 adrenergic receptor in the bladder to increase bladder capacity by relaxing the detrusor smooth muscle during bladder filling. Vibegron was studied in 2 phase 3, double-blind, placebo-controlled, randomized trials in adult patients with OAB, EMPOWUR and a second study by Yoshida, et al. (**Table 5**).[3,31] Patients in EMPOWUR had to meet the inclusion criteria of an OAB diagnosis by a physician while the second study enrolled patients with a history of OAB symptoms. The second study did not allow patients with uncontrolled hypertension, while EMPOWUR had no such exclusionary criteria. The mean patient age ranged from 59-63 years and a majority of participants were female (85-90%). Seventy percent of patients had a wet OAB diagnosis, defined as 1.0 or more UUI episodes per day, in both studies. EMPOWUR was comprised of predominately white participants (78%) while the second study enrolled Japanese patients. Only 14% percent of patients enrolled in EMPOWUR and 18% of patients in the second study had previously used pharmacotherapy for OAB, suggesting mild disease.[2,31] The primary endpoint in both trials was the mean number of daily micturitions. An additional co-primary endpoint in EMPOWUR was the average daily number of UUIs (in patients with wet OAB), which was a secondary endpoint in the second study.[3,.3] Additional secondary endpoints were daily urgency episodes, urgency incontinence episodes, and quality of life.

Both trials used a 2-week single-blind placebo run-in period and a 12-week double-blind treatment period. The EMPOWUR study (n=1,518) randomized patients to vibegron 75 mg, placebo or tolterodine ER in a 5:5:4 ratio by a central, web based interactive response system.[2] The second study randomized 1,224 patients in a 3.3:3.3:3.3:1 ratio to vibegron 50 mg, vibegron 100 mg, placebo or imidafenacin (only available in Japan).[3] In the EMPOWUR study patients recorded symptoms (e.g., micturitions, urgency, incontinence, and cause of incontinence) in a paper voiding diary (PVD) at baseline and at the end of treatment weeks 2, 4, 8 and 12. The second study recorded a 3-day micturition diary before each scheduled visit and the King's Health Questionnaire (KHQ) was administered at week 0 and week 12.[31] Patient satisfaction was measured via the Patient Global Impression (PGI) instrument.

Overall results suggest only mild to moderate efficacy of vibegron for the treatment of OAB. The average daily number of micturitions was reduced by -1.8 episodes in patients taking vibegron 75 mg compared to -1.3 episodes for patients taking placebo (LSMD -0.5; 95% CI, -0.8 to -0.2; P<0.001) in EMPOWUR and by -2.08 for vibegron 50 mg, -2.03 for vibegron 100mg, and -1.21 for placebo in the second study (p<0.001 for both doses of vibegron compared to placebo) (**Table 5**).[3] Results from a 52-week, double-blind extension study comparing vibegron to tolterodine support findings from the 12-week studies.[32] Reduction in micturitions demonstrated daily reductions for vibegron and tolterodine, -2.4 and 2.0, respectively (p-value not reported).[32] The MCID for reductions in average daily micturitions is -3.0 to -3.5 based on the Patient Global Impression (PGI) Severity Scale and -2.7 to -3.0 on the PGI-Frequency scale based on FDA analysis of

study data.[4] Reduction in micturitions of -0.5 to -0.86 a day demonstrated with vibegron compared to placebo would suggest that the change would not be clinically meaningful for most patients.

The second co-primary endpoint in EMPOWUR, average daily number of UUI episodes, was decreased with vibegron by -2.0 compared to -1.4 for placebo (p<0.001), with smaller reductions in the second study with a change of -1.35 in the vibegron 50 mg group, -1.47 in the vibegron 100 mg group and -1.08 for placebo (p=0.001 and p<0.001, respectively).[2,3] In patients with wet OAB, the proportion of wet OAB cases with 75% or greater reduction in average number of UUI episodes was higher with vibegron 75 mg compared to placebo, 52.4% versus 36.8%, respectively (P<0.001; ARR 15.6%/NNT 7).[2] Efficacy for the reduction in UUI episodes was sustained out to 52 weeks with decreases of -2.2 episodes in patients treated with vibegron 75 mg and -1.7 for tolterodine (p<0.05).[4]

For the bothersome symptom of frequency of daily urgency episodes, vibegron 75 mg decreased episodes by -2.7 a day from a baseline value of around 7.75 episodes a day.[2] This was in comparison to a decrease of -2.0 for placebo, which resulted in a statistically significant change, favoring vibegron, of LSMD -0.7 (95% CI, -1.1 to -0.2; P=0.0020), which is unlikely to be clinically impactful.[2] Results from the second study reiterate frequency findings with a reduction of -2.28 for vibegron 50 mg, -2.44 for vibegron 100 mg and -1.77 for placebo (P<0.001 for both comparisons).[3]

Quality of life outcomes were improved with vibegron compared to placebo. The OAB-q coping score, bother score and total score along with the PGI-severity score were secondary outcomes in EMPOWUR. Vibegron increased coping scores by 16.5 points compared to 12.9 points for placebo, (LSMD 3.6; 95% CI, 1.2 to 6.0; p=0.0039).[33] The HRQL total score was improved 14.6 points with vibegron and 10.8 with placebo (LSMD 3.8; 95% CI, 1.7 to 5.8; p<0.001). An improvement of around 3% is unlikely to be clinically impactful. Symptom bother scores were reduced -19.6 points with vibegron compared to -12.8 points with placebo (LSMD -6.9; 95% CI, -9.2 to -4.6; p<0.0001).[33] Both PGI-severity and PGI-control scores were reduced more with vibegron compared to placebo, -0.2 and -0.3 points, respectively (p<0.0001).[33] The second study found patients taking pharmacotherapy were “very much satisfied” based on the PGI more often than patients taking placebo; 59.5% for vibegron 50 mg, 62.0% for vibegron 100 mg and 37.1% for placebo.[31]

There is insufficient evidence to determine if vibegron is more effective than current treatment for OAB. In the EMPOWUR study tolterodine was used as an active control and imidafenacin was used as an active control in the second study. Daily reductions in mean micturition episodes were similar between vibegron 75 mg and tolterodine (-1.8 and -1.6, respectively) and vibegron 100 mg and imidafenacin (-2.03 and -2.06, respectively). These studies were not designed to detect statistical differences between the groups. Results would suggest minimal clinical differences, with no substantial benefit of vibegron over other therapy used for OAB.

Limitations to the findings include a placebo run-in which could select out patients that are more adherent to therapy. Patients who had no prior use of anticholinergics experienced the largest reduction in UUIs and accounted for the majority of patients enrolled in the study. In clinical practice anticholinergics are considered first-line pharmacotherapy and therefore the benefit seen outside the study setting would be expected to less than what was demonstrated in the trials. Manufacturer funding and authors with conflicts of interest may introduce additional bias. External validity is reduced due to high enrollment of white patients (78%) in the EMPOWUR study and inclusion of only Japanese patients in the second study. Additional details on trial methodology would have benefited the quality of both trials, EMPOWUR being a fair quality trial and the second study considered to be poor quality. FDA clinical evaluation of vibegron concluded that only some patients would have a clinically meaningful response to vibegron and vibegron is not considered more efficacious than currently available therapies.

Clinical Safety:

Summary of Clinical Safety:

Safety data from product labeling report the most common treatment-emergent adverse event (TEAEs) with vibegron occurring at a rate of 2% or more and higher than placebo, to be headache, diarrhea, nausea and upper respiratory infection (**Table 3**).[30] Treatment discontinuation due to adverse events were reported in 1.7% of patients treated with vibegron compared to 1.1% treated with placebo and 3.3% treated with tolterodine ER.[3] The most common reason for discontinuation was headache in the vibegron group and dry mouth in the tolterodine group. The incidence of severe adverse events was low in trials with one cerebrovascular accident in both vibegron 75 mg and tolterodine and one patient with pneumonia in both the vibegron 75 mg group and with placebo.[5] Severe adverse events occurring in only the vibegron 75 mg group include the following: abdominal pain (n=1), appendix disorder (n=1), atrial fibrillation (n=1), cardiac failure congestive (n=1), colitis (n=1), colorectal adenocarcinoma (n=1), noncardiac chest pain (n=1) and pleural effusion (n=1).[5] Blood pressure changes (mean maximum increase of approximately 3.5 mmHg systolic and 1.5 mmHg diastolic greater than placebo) experienced with mirabegron have not been demonstrated with vibegron (no clinically significant changes in blood pressure in clinical trials).[10,30]

Table 3. Adverse Reactions in Patients Treated with Vibegron Occurring in > 2% of Patients and Exceeding Placebo Rate[30]

Adverse Reaction	Vibegron 75 mg (n=545)	Placebo (n=540)
Headache	4%	2.4%
Nasopharyngitis	2.8%	1.7%
Diarrhea	2.2%	1.1%
Nausea	2.2%	1.1%
Upper respiratory tract infection	2.0%	0.7%

An extension study evaluating safety endpoints at 52 weeks of treatment found a low incidence of serious adverse events with vibegron therapy (0.4%) compared to tolterodine ER (0.9%).[32] Discontinuations due to study medications were 1.5% for vibegron and 3.4% for tolterodine ER. The most common adverse reactions were hypertension, 8.8% for vibegron and 8.6% for tolterodine ER, and urinary tract infection, 6.6% for vibegron and 7.3% for tolterodine ER.[32] Vibegron demonstrated an increased incidence in diarrhea compared to tolterodine ER, 4.8% versus 1.7% and upper respiratory infection, 3.7% versus 0.4%. Tolterodine ER had an increased risk of dry mouth (5.2%) compared to vibegron (1.8%).[32]

Vibegron increases the systemic exposure of digoxin and therefore digoxin concentrations should be monitored before and during concomitant therapy. No other notable drug interactions are associated with vibegron use. The use of vibegron is not recommended in patients with a eGFR <15 mL/min/1.73 m^2 (with or without dialysis) or in patients with severe hepatic impairment (Child-Pugh C).[30]

Safety data is limited by the small number of participants exposed to vibegron in clinical trials (n=3190), exclusion of patients with uncontrolled hypertension, and lack of data on patient comorbidities. Unanswered safety questions include the use in pediatric populations and in women who are pregnant or breast feeding. Post-marketing data has indicated safety concerns of urinary retention, rash/allergic skin reactions and constipation. Incidence and severity of these adverse events are unknown. Vibegron use beyond 52 weeks has not been studied.

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Reductions in daily micturitions
2) Reduction in urgency episodes
3) Urinary incontinence cure (wet OAB patients)
4) Urinary incontinence improvement (wet OAB patients)
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Average daily number of micturitions
2) Average daily number of urge urinary incontinence episodes

Table 4. Pharmacology and Pharmacokinetic Properties[30]

Parameter	
Mechanism of Action	Selective human beta-3 adrenergic receptor agonist. Activation of the beta-3 adrenergic receptor increases bladder capacity by relaxing the detrusor smooth muscle during bladder filling.
Oral Bioavailability	Not reported Food has no effect on absorption
Distribution and Protein Binding	Volume of distribution: 6304 L Protein binding: 50%
Elimination	59% fecal and 20% urine
Half-Life	30.8 hours
Metabolism	CYP3A4 is the most common enzyme responsible for in vitro metabolism. Metabolism plays a minor in the overall elimination of vibegron.

Table 5. Clinical Efficacy Evidence Table

Ref./ Study Design	**Drug Regimens/ Duration**	**Patient Population**	**N**	**Efficacy Endpoints**	**ARR/ NNT**	**Safety Outcomes**	**ARI/ NNH**	**Quality Rating Risk of Bias/Applicability**
1. Staskin, et al[3,4] EMPOWUR Phase III, MC, DB, PC	1. Vibegron 75 mg daily 2. Placebo daily 3. Tolterodine ER 4 mg daily	Demographics: Age: 62 yrs. old Female: 85% White: 78% U.S. sites: 90% Patients with wet OAB*: 77% Median micturitions/day: 10.51 Median urgency episodes/day: 7.92	ITT 1. 526 2. 520 3. 417 Attrition 1. 54 (10%) 2. 45 (8%) 3. 46 (11%)	**Co-Primary Endpoints:** Co-primary endpoint change from baseline to week 12: Average daily number of micturitions: 1. -1.8 episodes 2. -1.3 episodes 3. -1.6 episodes Vibegron vs. Placebo: LSMD -0.5 (95% CI, -0.8 to -0.2; P<0.001) Tolterodine ER vs. Placebo: LSMD -0.3 (95% CI, -0.6 to 0.1; P=0.0988)	 NA NS	Hypertension: 1. 9 (1.7%) 2. 9 (1.7%) 3. 11 (2.6%) Discontinuations due to adverse events: 1. 9 (1.7%) 2. 6 (1.1%) 3. 14 (3.3%)	NA for all	**Risk of Bias** (low/high/unclear): Selection bias: Low. Randomized in a 5:5:4 ratio by central, web based interactive response system. Stratified by sex and by wet vs. dry OAB. Baseline characteristics were well matched apart from patients in the vibegron group were slightly older and there were fewer male patients in the placebo group compared to the other groups. Double-dummy design was used to mask treatment allocation.

	2-week single-blind placebo run-in 12-week double-blind treatment period 4- week safety evaluation	Key Inclusion Criteria: - 18 years or older - History of OAB for at least 3 months and diagnosed by a physician - At least 75% meeting wet OAB criteria and up to 25% meeting dry OAB criteria Key Exclusion Criteria: - Urine output of greater than 3000 mls in 24 hours in past 6 months or in run-in phase - Lower urinary tract pathology that could be associated with urgency, frequency, or incontinence - History of surgery to correct stress urinary incontinence, pelvic organ prolapse, or procedural treatment for BPH within 6 months of screening - post-void residual volume of >150 mL - 3 or more UTIs per year		Average daily number of UUI episodes (wet OAB patients): 1. -2.0 episodes 2. -1.4 episodes 3. -1.8 episodes Vibegron vs. Placebo: LSMD -0.6 (95% CI, -0.9 to -0.3; P<0.001) Tolterodine ER vs. Placebo: LSMD -0.4 (95% CI, -0.7 to -0.1; P=0.0123) **Secondary Endpoint(s):** Frequency of daily urgency episodes: 1. -2.7 episodes 2. -2.0 episodes 3. -2.5 episodes Vibegron vs. Placebo: LSMD -0.7 (95% CI, -1.1 to -0.2; P=0.0020) Tolterodine ER vs. Placebo: LSMD -0.4 (95% CI, -0.9 to -0.0; P=0.0648) Proportion of wet OAB cases with 75% or greater reduction in average number of UUI episodes†: 1. 52.4% 2. 36.8% 3. 47.6% Vibegron vs. Placebo: (confidence interval not reported; P<0.001) Tolterodine ER vs. Placebo: (confidence interval not reported; P<0.05)	NA NA NA NS ARR 15.6/ NNT 7 ARR 10.8/ NNT 10	Serious adverse events: 1. 8 (1.5%) 2. 6 (1.1%) 3. 10 (2.3%) p-value not reported for safety outcomes		Performance bias: Unclear. Blinding of providers and investigators was stated but not clearly described. Detection bias: Unclear. Outcome assessment was not reported. Patient reported symptoms in diary and interpretation of results may be subject to bias. Attrition bias: Low. Attrition between groups was low and similar between groups. Data was analyzed based on FAS with multiple imputation for missing data. Reporting bias: High. Outcomes reported as prespecified; however, many outcomes that were evaluated (presented in FDA review) were not reported in published study. Other Bias: High. Manufacturer funded. All authors had conflicts of interest. **Applicability**: Patient: Results are most applicable to white females who are 65 years of age and older with wet OAB and treated in the US. Extensive exclusion criteria limiting applicability to many patient with OAB. Intervention: Vibegron dose of 75 mg was appropriate based on dosing studies. Comparator: Placebo comparator is appropriate; however, formal comparative analysis with tolterodine ER would help define vibegron place in therapy for the treatment of OAB. Outcomes: Outcomes used were appropriate for efficacy analysis of OAB treatments. Urinary incontinence cure rates for patients with wet OAB is an important outcome that was not reported. Quality of life is an important endpoint in patients with OAB and was evaluated but not reported in published study. Setting: This was a multi-center trial in 6 countries. Ninety percent of participants were from the U.S.

2. Yoshida, et al[31] Phase III, MC, DB, PC, PG	1. Vibegron 50 mg daily 2. Vibegron 100 mg daily 3. Placebo 4. Imidafenacin 0.1 mg twice daily 2-week placebo single-blind run-in 12-week double-blind treatment period	Demographics: Age: 59 yrs. old Female: 90% Japanese: 100% Patients with wet OAB*: 78% Previous OAB therapy: 18% Key Inclusion Criteria: - 20 years or older - History of OAB symptoms for 6 or more months - 8 or more micturitions a day and either 1 or more urgency episodes per day or 1 or more urgency incontinence episodes per day - Ability to use restroom without support - Normal ECG Key Exclusion Criteria: - Ruled out by study investigator - Cancer within 5 years - Systolic BP of 160 mmHg or greater, diastolic BP 100 or greater or pulse of 110 bpm or greater - Severe cardiac, liver, kidney or blood disorder - Unable to take anticholinergic or beta-adrenergic therapy - History of possible cause of urinary disorder - Post-void residual urine volume (PVR) of 100 ml or more	ITT 1. 370 2. 368 3. 369 4. 117 Attrition 1. 16 (4%) 2. 12 (3%) 3. 13 (4%) 4. 4 (3%)	**Primary Endpoint:** Change in mean number of micturitions/day from baseline at week 12: 1. -2.08 2. -2.03 3. -1.21 4. -2.06 Vibegron 50 mg vs. placebo: -0.86 (95% CI, -1.12 to -0.60; P<0.001) Vibegron 100 mg vs. placebo: -0.81 (95% CI, -1.07 to -0.55; P<0.001) **Secondary Endpoints:** Change from baseline in daily urgency episodes: 1. -2.28 2. -2.44 3. -1.77 4. -2.15 Vibegron 50 mg vs. placebo: -0.51 (95% CI, -0.76 to -0.25; P<0.001) Vibegron 100 mg vs. placebo: -0.67 (95% CI, -0.93 to -0.42: P<0.001) Change from baseline in daily urgency incontinence episodes: 1. -1.35 2. -1.47 3. -1.08 4. -1.51 Vibegron 50 mg vs. placebo: -0.27 (95% CI, -0.44 to -0.10; P=0.001) Vibegron 100 mg vs. placebo: -0.39 (95% CI, -0.55 to -0.22; P<0.001) Change from baseline in daily incontinence episodes: 1. -1.40 2. -1.53 3. -1.10	NA NA NA NA NA	Hypertension: 1. 0 (0%) 2. 0 (0%) 3. 0 (0%) 4. 2 (1.7%) Discontinuations due to adverse events: 1. 3 (0.8%) 2. 2 (0.5%) 3. 1 (0.3%) 4. 1 (0.9%) Serious adverse events: 1. 1 (0.3%) 2. 1 (0.3%) 3. 3 (0.8%) 4. 1 (0.9%) p-value not reported for safety outcomes	NA for all	**Risk of Bias** (low/high/unclear): Selection bias: Unclear. Randomized in a 3.3: 3.3: 3.3:1 ratio. Details not provided on strategy for randomization. Stratified by sex, prior OAB treatment, wet vs. dry OAB and mean micturitions at baseline. Treatment blinding was maintained by using a double-dummy design. Performance bias: Unclear. No details on blinding of providers and investigators were provided. Detection bias: Unclear. No details on binding of outcome assessors. Patient reported symptoms in diary and interpretation of results may be subject to bias. Attrition bias: Low. Attrition was low and similar between groups. Data was analyzed based on the FAS. No details on how missing data was handled. Reporting bias: Low. Outcomes reported as prespecified. Other Bias: High. Manufacturer funded. All authors had conflicts of interest. **Applicability**: Patient: The results of the study are most applicable to women with wet OAB that have not received previous drug therapy and are Japanese. Intervention: Vibegron 50 mg and 100 mg are appropriate dosing regimens. Comparator: Placebo comparator is appropriate; however, formal comparative analysis with imidafenacin would help define place in therapy for vibegron treatment of OAB. Outcomes: Outcomes used were appropriate for efficacy analysis of OAB treatments. Setting: One hundred and nine sites in Japan.

				4. -1.47 Vibegron 50 mg vs. placebo: -0.30 (95% CI, -0.49 to -0.12; P=0.001) Vibegron 100 mg vs. placebo: -0.43 (95% CI, -0.61 to -0.24; P<0.001) <u>Change from baseline in nocturia episodes:</u> 1. -0.58 2. -0.62 3. -0.47 4. -0.63 Vibegron 50 mg vs. placebo: -0.11 (95% CI, -0.21 to -0.02; P=0.016) Vibegron 100 mg vs. placebo: -0.16 (95% CI, -0.25 to -0.06; P=0.001) <u>Patients "very much satisfied" on PGI at week 12:</u> 1. 220 (59.5%) 2. 228 (62.0%) 3. 137 (37.1%) 4. 67 (57.3%) Vibegron 50 mg vs. placebo: 22.4% (95% CI, 15.3% to 29.4%; P<0.001) Vibegron 100 mg vs. placebo: 24.9% (95% CI, 17.8% to 31.8%; P<0.001)	NA NA NA NA NA NA			
<u>Abbreviations</u>: AC = active controlled; ARI = absolute risk increase; ARR = absolute risk reduction; BPH = benign prostatic hypertrophy; CI = confidence interval; DB = double-blind; ER = extended release; ITT = intention to treat; FAS = full analysis set; MC = multi-center; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = not significant; OAB = over active bladder; PC = placebo controlled; PG = parallel group; PP = per protocol; RR = relative risk; UTI = urinary tract infection; UUI = urge urinary incontinence. Key: * Wet OAB was defined as an average of 8.0 or more micturitions and 1.0 or more UUI episodes per day as determined during the run-in phase; † Results provided for patients with wet OAB								

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Appendix 1: Current Preferred Drug List

Generic	Brand	For	Route	PDL
fesoterodine fumarate	TOVIAZ	TAB ER 24H	ORAL	Y
oxybutynin	OXYTROL	PATCH TDSW	TRANSDERMAL	Y
oxybutynin chloride	OXYBUTYNIN CHLORIDE	SYRUP	ORAL	Y
oxybutynin chloride	DITROPAN XL	TAB ER 24	ORAL	Y
oxybutynin chloride	OXYBUTYNIN CHLORIDE ER	TAB ER 24	ORAL	Y
oxybutynin chloride	OXYBUTYNIN CHLORIDE	TABLET	ORAL	Y
darifenacin hydrobromide	DARIFENACIN ER	TAB ER 24H	ORAL	N
darifenacin hydrobromide	ENABLEX	TAB ER 24H	ORAL	N
flavoxate HCl	FLAVOXATE HCL	TABLET	ORAL	N
mirabegron	MYRBETRIQ	TAB ER 24H	ORAL	N
oxybutynin	OXYTROL FOR WOMEN	PATCH TD 4	TRANSDERMAL	N
oxybutynin chloride	GELNIQUE	GEL PACKET	TRANSDERMAL	N
solifenacin succinate	VESICARE LS	ORAL SUSP	ORAL	N
solifenacin succinate	SOLIFENACIN SUCCINATE	TABLET	ORAL	N
solifenacin succinate	VESICARE	TABLET	ORAL	N
tolterodine tartrate	DETROL LA	CAP ER 24H	ORAL	N
tolterodine tartrate	TOLTERODINE TARTRATE ER	CAP ER 24H	ORAL	N
tolterodine tartrate	DETROL	TABLET	ORAL	N
tolterodine tartrate	TOLTERODINE TARTRATE	TABLET	ORAL	N
trospium chloride	TROSPIUM CHLORIDE ER	CAP ER 24H	ORAL	N
trospium chloride	TROSPIUM CHLORIDE	TABLET	ORAL	N
vibegron	GEMTESA	TABLET	ORAL	N

Appendix 2: Medline Search Strategy

Database(s): Ovid MEDLINE(R) ALL 1946 to April 21, 2021
Search Strategy:

#	Searches	Results
1	oxybutynin.mp.	1597
2	fesoterodine.mp.	281
3	darifenacin.mp.	358
4	flavoxate.mp. or Flavoxate/	190
5	mirabegron.mp.	639
6	solifenacin.mp. or Solifenacin Succinate/	779
7	tolterodine.mp. or Tolterodine Tartrate/	1097
8	trospium.mp.	328
9	vibegron.mp.	37
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	3826
11	limit 10 to (english language and humans and yr="2018 -Current")	331
12	limit 11 to (clinical trial, phase iii or meta analysis or practice guideline or "systematic review")	41

Appendix 3: Prescribing Information Highlights

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

GEMTESA (vibegron) tablets, for oral use
Initial U.S. Approval: 2020

----------INDICATIONS AND USAGE----------
GEMTESA is a beta-3 adrenergic agonist indicated for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency in adults (1)

----------DOSAGE AND ADMINISTRATION----------
- The recommended dose is one 75 mg tablet once daily. (2.1)
- Swallow tablet whole with water. (2.1)
- Tablet may be crushed and mixed with applesauce. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 75 mg (3)

----------CONTRAINDICATIONS----------
Do not use if prior hypersensitivity reaction to vibegron or any components of the product. (4)

----------WARNINGS AND PRECAUTIONS----------
Urinary Retention: Monitor for urinary retention, especially in patients with bladder outlet obstruction and also in patients taking muscarinic antagonist medications for OAB, in whom the risk of urinary retention may be greater. If urinary retention develops, discontinue GEMTESA. (5.1)

----------ADVERSE REACTIONS----------
Most common adverse reactions (≥2%) reported with GEMTESA were headache, urinary tract infection, nasopharyngitis, diarrhea, nausea, and upper respiratory tract infection. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Urovant Sciences, Inc., at 1-833-876-8268 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
Digoxin: Measure serum digoxin concentrations before initiating GEMTESA. Monitor serum digoxin concentrations to titrate digoxin dose to desired clinical effect. (7)

----------USE IN SPECIFIC POPULATIONS----------
Pediatric use: Safety and effectiveness in pediatric patients have not been established. (8.4)
End-stage Renal Disease with or without Hemodialysis: Not recommended. (8.6)
Severe Hepatic Impairment: Not recommended. (8.7)

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

Revised: 12/2020

Appendix 4: Key Inclusion Criteria

Population	Patients with overactive bladder
Intervention	Antimuscarinic and beta-3 adrenergic agonists
Comparator	Active treatment or placebo
Outcomes	Daily micturitions, urgency episodes, urinary incontinence, safety and quality of life
Setting	Outpatient

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
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Drug Effectiveness Review Project Summary Report – Biologics in Asthma

Date of Review: August 2021

Date of Last Review: July 2018 & July 2019 (dupilumab)
Literature Search: 08/07/20-5/01/21

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

Research Questions:
1. What is the efficacy for the monoclonal antibodies approved for the treatment of eosinophilic asthma which include: benralizumab, dupilumab, mepolizumab, and reslizumab?
2. What is the tolerability and frequency of adverse events (AEs) for benralizumab, dupilumab, mepolizumab, and reslizumab in the treatment of eosinophilic asthma?
3. What is the evidence on the benefits and harms of using omalizumab to treat patients with moderate-to-severe allergic asthma?
4. Are there subgroups of patients (e.g. groups defined by demographics, asthma severity, comorbidities) for which monoclonal antibodies used to treat asthma differ in efficacy, or frequency of adverse events?

Conclusions:
DERP Report
- The Drug Effectiveness Review Project (DERP) identified 44 randomized clinical trials (RCTs) in 52 publications that reported on the use of 5 monoclonal antibodies for asthma management.[1] Eighteen new trials were identified for the 2021 update. Most of the trials compared the monoclonal antibody to placebo while maintaining standard background therapy with an asthma controller, rescue therapy or oral corticosteroids.[1] Most of the RCTs evaluating the effectiveness of add-on therapy generally enrolled or primarily reported outcomes for the participants with the allergic asthma phenotype; thus, the applicability of findings to other asthma phenotypes is not certain.[1] Eight studies were rated as having a high risk of bias for various methodological issues; the rest were rated as having a moderate risk of bias, typically due to extensive manufacturer involvement in study design, execution, and reporting.[1] No head-to-head studies were identified for this report.[1] Data on safety and effectiveness beyond 56 weeks is not available.[1] In addition to standard measures of symptom control and quality of life, studies evaluating asthma commonly reported on the impact of treatment on asthma exacerbations and reduction in corticosteroid usage.[1] Although many statistically significant differences across studies and outcomes were observed, the average magnitude of some differences may not be clinically relevant, as the minimal clinically important difference (MCID) was not achieved.[1]
- A range of very low to high quality evidence (depending on drug) suggests that for people with asthma, benralizumab, dupilumab, mepolizumab, omalizumab, and reslizumab are more effective than placebo for controlling symptoms as evaluated by achieving an MCID of 0.5 points on the Asthma

Control Questionnaire (ACQ) over the duration of the trials (12 to 56 weeks).[1] Data from 3 add-on efficacy RCTs showed benralizumab was more effective compared to placebo as measured by the proportion of patients achieving an MCID of 0.5 points at 12 to 24 weeks on the ACQ (pooled risk ratio [RR], 1.17; 95% confidence interval [CI], 1.06 to 1.28; high quality of evidence [QoE]).[1] Data from 1 add-on efficacy RCT showed dupilumab was more effective then placebo as measured by the proportion of participants achieving an MCID of 0.5 points on the ACQ (RR, 1.22; 95% CI, 1.06 to 1.40; moderate QoE).[1] Two add-on efficacy RCTs and 1 steroid-sparing RCT demonstrated mepolizumab was more effective compared with placebo as measured by difference in mean change from baseline on ACQ (range of estimates, -0.43 to -0.52; moderate QoE).[1] Very low quality evidence from 2 add-on efficacy RCTs showed omalizumab was more effective than placebo as measured by the difference in mean change from baseline on the ACQ; findings were mixed regarding achieving an MCID of 0.5 points (range of estimates, 0 to -0.87).[1] High quality evidence from 4 add-on efficacy RCTs demonstrated reslizumab was more effective than placebo as measured by the proportion of participants achieving an MCID of 0.5 points on the ACQ (range of pooled RRs, 1.24 [95% CI 1.13 to 12.35] to 1.28 [95% CI 1.08 to 1.52] from 4 add-on efficacy trials at 15 to 52 weeks, respectively).[1]

- Moderate to high QoE (depending on drug) suggests benralizumab, dupilumab, mepolizumab, omalizumab, and reslizumab were more effective than placebo for reducing asthma exacerbations.[1] Data from 3 add-on efficacy RCTs showed benralizumab was more effective compared to placebo as measured by incidence of exacerbations (pooled RR, 0.75; 95% CI, 0.65 to 0.89; moderate QoE).[1] Moderate quality evidence from 2 add-on efficacy RCTs and 1 steroid-sparing RCT showed dupilumab was more effective then placebo as measured by annualized rate of severe exacerbations (incident rate ratio [IRR], 0.30; 95% CI, not reported [NR]).[1] Data from 2 add-on efficacy RCTs and 1 steroid-sparing RCT showed mepolizumab was more effective as measured by annualized rate of exacerbations (IRR range, 0.42 [95% CI 0.31 to 0.56] to 0.68 [95% CI 0.47 to 0.99]; moderate QoE).[1] Twelve add-on efficacy RCTs and 4 steroid-sparing RCTs demonstrated omalizumab was more effective compared to placebo as measured by the incidence of exacerbations (pooled RR, 0.71; 95% CI, 0.61 to 0.82 for add-on efficacy trials; range of pooled RRs, 0.57; [95% CI 0.46 to 0.67 for steroid reduction phase] to 0.64; [95% CI 0.51 to 0.77 for steroid stable phase]) in steroid-sparing RCTs; high QoE).[1] Three add-on efficacy RCTs showed reslizumab was more effective compared to placebo as measured by annualized rate of exacerbations (pooled IRR, 0.53; 95% CI, 0.36 to 0.71; high QoE).[1]
- Low to high QoE (depending on drug) suggests benralizumab, dupilumab, mepolizumab, and omalizumab reduce corticosteroid use in people with asthma compared to placebo.[1] In 1 steroid-sparing RCT, benralizumab every 4 weeks was more effective compared to placebo as measured by the proportion of participants reducing oral maintenance oral steroid dose by 50% or more (RR, 1.79; 95% CI, 1.28 to 2.50; moderate QoE).[1] One steroid-sparing RCT showed dupilumab was more effective compared to placebo at reducing the use of maintenance corticosteroids as measured by 50% or greater reduction in corticosteroid dose (calculated RR 1.49; 9% CI 1.22 to 1.83; moderate QoE).[1] Low quality evidence from 1 steroid-sparing RCT demonstrated mepolizumab was more effective compared to placebo as measured by the proportion of participants able to reduce oral steroid doses by 50% or more (RR, 1.61; 95% CI, 1.07 to 2.41).[1] High quality evidence from 3 steroid-sparing RCTs revealed omalizumab was more effective than placebo as measured by the proportion of participants who reduced their maintenance inhaled steroid dose by 50% or more (pooled RRs range, 1.39 to 1.40 across various steroid trial phases: steroid-stable, steroid-reduction, and extension).[1] However, no difference in corticosteroid use was observed for reslizumab compared to placebo (difference in mean percentage steroid dose change, -17.8; 95% CI, -39.0 to 3.5; low QoE).[1]
- The evidence suggests either fewer adverse effects (AEs) with the monoclonal antibodies, or no difference in events, compared to placebo (moderate to high QoE, depending on drug) in patients with asthma.[1] Fewer adverse events occurred among participants allocated to benralizumab compared to placebo (7 RCTs; pooled RR, 0.94; 95% CI, 0.90 to 0.98; moderate QoE).[1] No significant difference between dupilumab and placebo in the incidence of adverse events was detected (4 RCTs; pooled RR, 0.99; 95% CI, 0.95 to 1.03; high QoE).[1] Fewer events occurred among participants allocated to mepolizumab versus placebo (pooled RR, 0.93; 95% CI, 0.88 to 0.99; high QoE).[1] No difference in events was observed between omalizumab and placebo (17 RCTs; pooled RR, 1.00; 95% CI, 0.97 to 1.03; high QoE).[1] No difference in events was detected between reslizumab and placebo (7 RCTs; pooled RR, 0.92; 95% CI, 0.84 to 1.00; high QoE).[1] Specific AEs associated with monoclonal antibody administration were not discussed in the DERP report, nor were absolute rates of AEs.

- The evidence suggests benralizuamb, dupilumab, mepolizumab, omalizumab and reslizumab are more effective than placebo for treatment of asthma among children, adolescents and adults.[1] No additional subgroups were identified for this report.[1]
- Thirteen RCTs of monoclonal therapies for asthma are ongoing, including 1 head-to-head study comparing omalizumab to mepolizumab.[1]

New Indications

- Mepolizumab received FDA-approval in September 2020 for the treatment of adult and pediatric patients aged 12 years and older with hypereosinophilic syndrome (HES) with a duration of 6 months or greater without an identifiable non-hematologic secondary cause.[2]
- In November 2020 omalizumab received FDA-approval for treatment of nasal polyps in adult patients 18 years of age and older with inadequate response to nasal corticosteroids, as add on maintenance treatment.[3]

New Formulations

- Mepolizumab and omalizumab are FDA-approved as pre-filled syringes for self-subcutaneous administration.[2,3]

Recommendations:

- Recent evidence summarized in the Drug Effectiveness Review Project (DERP) report for the asthma biologic medications does not support specific changes to the current Preferred Drug List (PDL).
- Create a PDL class entitled "Biologics for Severe Asthma" and include benralizumab, dupilumab, mepolizumab, omalizumab and reslizumab in this PDL class.
- Modify "Monoclonal Antibodies for Severe Asthma" Prior Authorization (PA) criteria to include expanded indications for mepolizumab in treatment of HES and omalizumab for treatment of nasal polyps.
- Retire current dupilumab PA criteria. Add dupilumab to "Monoclonal Antibodies for Severe Asthma" PA criteria.
- Extend PA criteria to physician administered drugs for all monoclonal antibodies used to treat asthma.

Summary of Prior Reviews and Current Policy

A drug class update focused on asthma and COPD maintenance medications was presented to the Pharmacy & Therapeutics (P & T) Committee at the October 2020 meeting. A class update focused solely on monoclonal antibodies (i.e., biologics) used to treat asthma was presented at the July 2018 P & T meeting. Recommendations for the July 2018 presentation were informed by the April 2018 report researched by the DERP .[4] The Oregon Health Plan (OHP) provides coverage through PA criteria for 4 biologic agents approved to manage eosinophilic asthma refractory to other asthma therapies: benralizumab, dupilumab, mepolizumab, and reslizumab. Mepolizumab is also Food and Drug Administration (FDA)-approved for treatment of adults with eosinophilic granulomatosis with polyangiitis (EGPA). Dupilumab has additional FDA-approved indications including treatment of atopic dermatitis in adolescents and adults and as maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP).[5] An additional biologic agent (omalizumab), is also part of the monoclonal antibodies for asthma PA criteria and provides coverage for patients with severe allergic asthma. Omalizuamb is also indicated for management of chronic urticaria; however, according to the Health Evidence Review Commission (HERC) prioritized list, this diagnosis is not funded. Current criteria require that auto-injectable epinephrine be co-prescribed with all asthma biologics due to the risk of delayed anaphylaxis. There are no preferred monoclonal antibodies for asthma. During the first quarter of 2021 the only asthma biologic agents billed through point of sale pharmacy claims in the fee-for-service (FFS) population were omalizumab with 1 claim and mepolizumab with 4 claims. On average, fewer than 24 claims per quarter were billed as provider administered drugs in 2020.

Methods:
The February 2021 drug class report on Biologic Drugs to Treat Asthma and Chronic Spontaneous Urticaria by the DERP was used to inform recommendations for this class update.[1]

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

Background:
Asthma is a heterogeneous disease, characterized by chronic airway inflammation which results in bronchial hyper-responsiveness.[6] It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.[6] The long-term goals of asthma management are to achieve good symptom control, and to minimize future risk of asthma-related mortality, exacerbations, persistent airflow limitation, and side-effects of treatment.[6] According to the 2020 Global Initiative for Asthma (GINA) guidelines, asthma severity is classified according to symptoms and level of treatment required to control exacerbations.[6] Intermittent, mild asthma (Step 1) is well controlled with low dose inhaled corticosteroid (ICS) therapy in combination with long-acting beta-agonists (LABAs).[6] The preferred Step 2 treatment includes daily low-dose ICS with as-needed short-acting beta-agonists (SABAs) in children or in fixed-dose combination with LABAs for adults and adolescents.[6] Daily leukotriene receptor antagonists (LTRAs) are alternative options for Step 2 in those patients who are unable or unwilling to use ICS.[6] Preferred Step 3 controller options for adults and adolescents with moderate asthma include low- or medium-dose ICS-LABA with or without as-needed SABAs or the addition of a LTRA.[6] For children, the preferred Step 3 controller options include a medium-dose ICS or low-dose ICS-LABAs combination.[6] The preferred Step 4 treatment for severe asthma varies depending on what has been tried for Step 3, but often includes low- or medium-dose ICS-LABAs with additional controllers, including LTRAs or tiotropium, with SABAs as needed.[6] The 2020 GINA guidelines recommend a monoclonal antibody for patients with severe asthma unresponsive to controller-drug treatments (Step 5).[6] Severe asthma is reported to account for about 5 to 10 percent of the total asthma population, but exact prevalence is unknown due to heterogeneity in presentation of severe asthma.[7] Although the prevalence of severe asthma is relatively low, it accounts for 50% of the health care costs associated with managing exacerbations.[8]

Recognizable clusters of demographic, clinical and/or pathophysiological characteristics are often called asthma phenotypes.[6] In patients with more severe asthma, some phenotype-guided treatments are available.[6] Phenotyping severe asthma based on demographic or clinical characteristics may help to effectively target treatment. More recently, individual treatment has been geared toward treating the specific asthma phenotype, which includes allergic, nonallergic, exercise-induced, fixed-obstruction, and occupational asthma.[9] Allergic asthma is the most common phenotype, describing between 40% and 50% of cases, and can be identified through allergy testing for environmental allergens, eosinophilia, blood immunoglobin E (IgE) levels, and exhaled nitric oxide testing.[1] Patients with eosinophilic asthma also have high levels of sputum eosinophils, and while a correlation of blood eosinophil levels to sputum eosinophils is not well defined, guidelines define the threshold as blood eosinophils of ≥150 cells/µL.[6] Studies of biologic therapies have evaluated use in patients with eosinophil levels of greater than 150 cells per µL to more than 400 cells per µL.

Omalizumab is an anti-immunoglobulin E (IgE) monoclonal antibody that has been available for over a decade to manage severe allergic asthma and chronic urticaria. Three additional monoclonal antibodies; mepolizumab, reslizumab, and benralizumab, mediate the effects of interleukin (IL)-5 and are effective in management of eosinophilic asthma as add on therapy. Interleukin-5 is critical for eosinophil maturation and activation. Activated eosinophils can increase

airway smooth muscle contraction and mucous secretion. The monoclonal antibodies that mediate IL-5 activity are FDA-approved to treat severe asthma in patients with an eosinophilic phenotype of asthma. Safety and efficacy of these agents have not been assessed in head-to-head trials. Dupilumab, an IL-4 receptor antagonist, is also indicated as add on maintenance therapy for moderate to severe asthma.

Although the biologic agents used to manage severe asthma are well-tolerated, serious adverse reactions have been reported. Anaphylaxis has been reported in 0.3% of patients receiving reslizumab; therefore, the drug carries an FDA boxed warning recommending observation after infusion.[10] Hypersensitivity reactions have been observed with mepolizumab and benralizumab; however neither drug has a boxed warning regarding anaphylaxis.[2,11] There are notable differences between each biologic agent approved to treat asthma primarily related to the age of administration, route of administration, dosing regimen, and FDA-approved indication. **Table 1** summarizes significant prescribing information for the 5 biologic agents with FDA approval to treat moderate to severe asthma.

Table 1. Monoclonal Antibodies FDA-Approved to Manage Moderate to Severe Asthma[2,3,5,10,11]

Generic Name	Brand Name	FDA Approval Year	Target	FDA Approved Indication	Maintenance Dose and Administration Route	FDA Approved Administration Age for Asthma	FDA Boxed Warning	Blood Eosinophil Levels in Clinical Trials in Primary Analysis Population
Dupilumab	DUPIXENT	2018	IL-4 Receptor	Add on maintenance treatment for moderate to severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma	Adults and Adolescents: 200 to 300 mg SC every 2 weeks	≥ 12 yo	No	Subjects enrolled in clinical trials without requiring a minimum baseline blood eosinophil count
Benralizumab	FASENRA	2017	IL-5 Receptor	Severe asthma with an eosinophilic phenotype	30 mg SC every 8 weeks	≥ 12 yo	No	≥300 cells/µL
Reslizumab	CINQAIR	2016	IL-5	Severe asthma with an eosinophilic phenotype	3 mg/kg IV infusion every 4 weeks	≥ 18 yo	Yes: for possible anaphylaxis	≥ 400 cells/µL
Mepolizumab	NUCALA	2015	IL-5	Severe asthma with an eosinophilic phenotype	Ages ≥ 6 yo: 40 mg SC every 4 weeks Ages ≥ 12 yo: 100 mg SC every 4 weeks	≥ 6 yo	No	≥ 150 cells/µL at screening or ≥ 300 cells/µL in the previous year
Omalizumab	XOLAIR	2003	IgE	Moderate to severe persistent asthma	75 to 375 mg SC every 2 to 4 weeks based on weight and serum IgE levels	≥ 6 yo	Yes: for possible anaphylaxis	Not Applicable

Abbreviations: FDA = Food and Drug Administration; IgE = immunoglobulin E; IL = interleukin; IV = intravenous; SC = subcutaneous; YO = years old								

Clinically relevant outcomes to assess treatments of severe asthma include reduction in asthma exacerbations that result in: 1) decreased emergency department (ED) visits or hospitalizations; 2) decreased chronic use of oral corticosteroids; 3) improved quality of life; or 4) improved symptom management. Several instruments are commonly used in clinical trials to assess quality-of-life and symptom management related to asthma. These tests are self-administered and subject to recall bias but have been validated with highly consistent reproducibility between users. The Asthma Control Questionnaire (ACQ) is a 5-item questionnaire that assesses asthma symptoms and rescue inhaler use in the preceding week.[12] Scores range from 0 (totally controlled) to 6 (severely uncontrolled), with a change in score of 0.5 units the MCID.[13] An ACQ score consistently greater than 1.5 indicates poor symptom control.[13] The Asthma Quality of Life Questionnaire (AQLQ) contains 32 items assessing disease-specific, health-related quality-of-life that include domains of activity limitations, symptoms, emotional function, and environmental stimuli with a 2-week recall.[1] The scale ranges from 1 (severely impaired) to 7 (not impaired at all). Total and domain scores are calculated by taking the mean of all questions overall or for each domain.[1] The MCID for this tool is 0.5 points for each item.[1] The St. George's Respiratory Questionnaire (SGRQ) was developed to measure health in chronic health airflow limitation.[14] The questionnaire is a 50 or 76 item assessment (depending on version) that includes 2 domains: frequency and severity of symptoms and impact on activities, which can be used with a 1-month, 3-month, or 12-month recall.[1] The scale ranges from 0 (no symptoms/limitations) to 100 (severe symptoms/ limitations).[1] Scoring varies by item and item scores are converted into a domain score and an overall score, both reported on the same scale.[1] The MCID for the SGRQ is 4 points.[1] The Asthma Control Test (ACT) contains 5 self-reported items related to symptoms and daily functioning over past 4 weeks used in patients aged 12 years and older.[1] Assessments include shortness of breath and general asthma symptoms, use of rescue medications, effect of asthma on daily functioning, and overall self-assessment of asthma control.[1] The scale ranges from 5 (poor control) to 25 (complete control) with scores of 19 and greater indicating well-controlled asthma.[1] Each item is scored on 5-point Likert scale and the sum of scores across all items yields the total score.[1] The MCID for the ACT is 3 points.[1] A summary of the outcomes discussed in the DERP report is presented in **Table 2.**

Table 2. Summary of Outcome Measures for Asthma[1]

Measure	Scale	Minimal Clinically Important Difference (MCID)
Asthma Control Questionnaire (ACQ)	0 (totally controlled) to 6 (severely uncontrolled)	0.5
Asthma Control Test (ACT)	5 (poor control) to 25 (complete control)	3
Asthma Quality of Life Questionnaire (AQLQ)	1 (severely impaired) to 7 (not impaired at all)	0.5
Pediatric Asthma Quality of Life Questionnaire (PAQLQ)	1 (severely impaired) to 7 (not impaired at all)	0.5
St. George's Respiratory Questionnaire (SGRQ)	0 (no symptoms/limitations) to 100 (severe symptoms/limitations)	4

Change from baseline in forced expiratory volume is a common surrogate endpoint used in asthma treatment trials since it is highly reproducible. A decline in lung function is observed when forced expiratory volume in 1 second [FEV_1] is 60% or less of predicted values or peak expiratory flow shows a 30% or greater decrease from baseline.[1]

Summary DERP Report Findings:
The 2021 DERP report focuses on adults and children with moderate to severe asthma or chronic spontaneous urticaria (CSU).[1] Because CSU is not funded by HERC, this class update will focus on evidence identified for asthma management. Randomized trials that evaluated the effectiveness and safety of benralizumab, dupilumab, mepolizumab, omalizumab, and reslizumab in treating patients with asthma were included in the DERP report.[1] Eligible comparators included active treatment with another FDA-approved biologic, placebo, or usual care. Eligible outcomes for asthma included measures of symptom control, quality of life, oral steroid use, severe exacerbations requiring emergency department (ED) or hospital admission, all-cause ED or hospital admission, and mortality.[1]

The literature search for the recently issued DERP report was conducted from August 2017 through December 2020.[1] A previous DERP systematic review on biologics for asthma included existing systematic reviews and only included primary studies if they were not covered within an existing systematic review.[4] The 2021 DERP update relies entirely on primary RCTs and only used the previous DERP review to identify potentially eligible studies conducted before the most recent literature search. A total of 44 RCTs with 18 new studies reported on the use of biologics for asthma.[1] All but 3 RCTs used placebo controls. Two RCTs used a "best standard of care" control, and 1 RCT used a no-treatment control group.[1] No studies evaluating head-to-head comparisons were identified. Seven RCTs evaluated benralizumab, 4 RCTs evaluated dupilumab, 3 RCTs evaluated mepolizumab, 7 RCTs evaluated reslizumab, and 23 RCTs evaluated omalizumab.[1] All but 1 RCT reported effectiveness outcomes, and all but 3 RCTs reported safety outcomes.[1] Specific AEs and serious adverse events (SAEs) associated with monoclonal antibody administration were not discussed in the DERP report.

Eight studies were rated as having a high risk of bias for various methodological issues; the rest were rated as having a moderate risk of bias, typically due to extensive manufacturer involvement in study design, execution, and reporting.[1] Most trials evaluated the add-on efficacy of the biologic drug compared to placebo or control while maintaining standard background asthma controller and rescue therapy in both groups.[1] A fewer number of studies evaluated the add-on efficacy of the biologic drug compared to placebo while tapering inhaled or oral maintenance corticosteroids (or other controller treatment) in both groups.[1] Outcomes were reported between 12 and 56 weeks of duration.[1]

The risk of bias for the included RCTs was evaluated using specific parameters. Low-risk-of-bias RCTs included a clear description of the population, setting, intervention, and comparison groups; a random and concealed allocation of patients to study groups; low dropout rates; and intention-to-treat analyses.[1] Low-risk-of-bias randomized controlled trials also had low potential for bias from conflicts of interest and funding source(s).[1] Moderate-risk-of-bias RCTs had incomplete information about methods that might mask important limitations or a meaningful conflict of interest.[1] High-risk-of-bias RCTs had clear flaws that could introduce significant bias.[1]

Key Findings for Benralizuamb Compared to Placebo
Seven industry-sponsored RCTs evaluated 1 or more dosing regimens of benralizumab compared to placebo (SIROCCO,[15] BISE,[16] CALIMA,[17] ANDHI,[18] Park et al.,[19] SOLANA,[20] and ZONDA[21]). All 7 RCTs were multicenter, international studies; 6 studies were phase 3 trials, whereas Park et al. was a phase 2 trial.[1] The CALIMA and SIROCCO trials enrolled participants aged 12 and older; all other studies only enrolled adults.[1] Six studies required participants to be taking moderate- to high-dose ICS; only the BISE trial enrolled persons taking low- to moderate-dose ICS.[1] Four trials (ANDHI, SOLANA, ZONDA, and Park et al.) enrolled only

participants with allergic asthma while SIROCCO did not limit enrollment to persons with allergic asthma but reported all results by subgroup based on baseline eosinophil level (less than 300 cells per µL versus 300 cells per µL and greater).[1] CALIMA did not limit enrollment to persons with allergic asthma, but only reported findings among the 56% of enrolled persons with eosinophils of 300 cells per µL and greater, which was reported as the primary group of interest.[1] The BISE trial enrolled persons with and without allergic asthma but did not report the findings separately.[1] The study populations, interventions, and outcomes are summarized in **Table 3**.

Symptom Control

- Pooled estimates from 3 add-on efficacy RCTs (N = 1,100)[16,18,20] showed benralizumab was more effective compared to placebo for improving symptom control as measured by the proportion of subjects achieving a MCID of 0.5 points on the ACQ at 12 to 24 weeks (pooled RR] 1.17; 95% CI, 1.06 to 1.28); high QoE.[1]

Quality of Life

- Data from 1 add-on efficacy RCT (N = 211)[16] demonstrated benralizumab was no different in in improving quality of life compared to placebo as measured by the proportion of subjects achieving a minimally important change of 0.5 points on the AQLQ at 12 weeks (43% vs. 32% respectively; calculated RR 1.34; 95% CI, 0.94 to 1.90); low QoE.[1]

Exacerbations

- Data from 4 add-on efficacy RCTs (N = 2,233)[15,16,18,19] were pooled to assess exacerbation rates. The analysis showed benralizumab was more effective than placebo in lowering the annualized rate of exacerbations (pooled IRR 0.59; 95% CI, 0.47 to 0.79 for every 4 week dose; IRR 0.55; 95% CI, 0.43 to 0.67 for every 8 week dose; absolute rates NR); moderate QoE.[1]
- Pooled data from 2 add-on efficacy RCTs (N = 1,537)[15,17] showed benralizumab was more effective over placebo in reducing annualized rate of exacerbations requiring ED or hospital visits only for the 4 week dose, findings for the 8 week dose were too heterogenous to pool (pooled IRR, 0.67; 95% CI, 0.38 to 0.96 for every 4-week dose; absolute rates NR); low QoE.[1]

Corticosteroid Use

- In 1 steroid-sparing RCT (N = 220)[21] benralizumab was more effective compared to placebo for reducing the proportion of participants with a 50% reduction in their maintenance oral corticosteroid dose at 28 weeks of follow-up (calculated RR 1.79; 95% CI, 1.28 to 2.50 for every 4 week dose; calculated RR 1.76; 95% CI, 1.26 to 2.47 for every 8 week dose); moderate QoE.[1]

Overall Adverse Effects and Serious Adverse Effects

- Pooled analysis of the 7 RCTs listed in **Table 3** (N = 2,897) revealed fewer AEs occurred among participants allocated to benralizumab versus placebo (pooled RR, 0.94; 95% CI, 0.90 to 0.98); high QoE.[1] Pooled analysis of the 7 RCTs also showed fewer serious adverse events (SAEs) occurred among participants allocated to benralizumab versus placebo (pooled RR, 0.76; 95% CI, 0.61 to 0.96) based on moderate QoE (downgraded for imprecision due to the rarity of observed events).[1]

Mortality

- Six of the 7 studies also reported mortality; however, events were rare (12 deaths of 2,008 total participants across studies [0.60%]); thus, estimates of treatment effect were imprecise.[1]

Table 3. Randomized Controlled Trials of Benralizumab in Patients with Asthma[1]

Trial Citation Trial Name Study Design Risk of Bias	Population	Intervention (n) Comparator (n) Co-interventions	Outcomes Assessed (Primary Designated Outcome)
Bleecker et al.[15] SIROCCO Phase 3 RCT of add-on therapy Moderate	• Subjects aged 12 to 75 • Treatment with medium- to high-dose ICS and LABA • At least 2 exacerbations requiring systemic steroids in prior year • ACQ score ≥ 1.5 • Subjects with allergic asthma (67%) and non-allergic asthma (33%)	• Benralizumab 30 mg SC every 4 wks (n = 399) • Benralizumab 30 mg SC every 8 wks (n = 398) • Placebo (n = 407) Continued stable doses of other asthma controllers, SABA rescue for symptoms	At 48 weeks: • Symptom control • QoL • Adverse events • Mortality (Annualized exacerbation rate)
Ferguson et al.[16] BISE Phase 3 RCT of add-on therapy Moderate	• Subjects aged 18 to 75 • Low- to medium-dose ICS with or without other controller medications • Evidence of uncontrolled symptoms • Subjects with allergic (30%) and non-allergic asthma (70%)	• Benralizumab 30 mg SC every 4 wks (n = 106) • Placebo (n = 105) Controller ICS converted to standardized doses, LABAs withdrawn at enrollment, SABA rescue for symptoms	At 12 weeks: • Symptom control • QoL • Exacerbations • Adverse events • Mortality (FEV_1 change)
FitzGerald et al.[17] CALIMA Phase 3 RCT of add-on therapy Moderate	• Subjects aged 12 to 75 • Treatment with medium- to high-dose ICS and LABA • At least 2 exacerbations requiring systemic steroids in prior year • ACQ score ≥ 1.5 • Subjects with allergic (56%) and non-allergic asthma (44%)	• Benralizumab 30 mg SC every 4 wks (n = 425) • Benralizumab 30 mg SC every 8 wks (n = 441) • Placebo (n = 440) Continued stable doses of other asthma controllers, SABA rescue for symptoms	At 56 weeks: • Symptom control • QoL • Exacerbations • Adverse events • Mortality (Annualized exacerbation rate in subgroup with eosinophils > 300/µL)
Harrison et al., 2020[18] ANDHI Phase 3 RCT of add-on therapy Moderate	• Subjects aged 18 to 75 • Treatment with high-dose ICS plus another asthma controller • Blood eosinophil count at least 150/µL • ≥ 2 exacerbations in prior year • ACQ score ≥ 1.5	• Benralizumab 30 mg SC every 4 wks first 3 doses, then every 8 wks (n = 427) • Placebo (n = 229) Continued stable doses of other asthma controllers	At 24 weeks: • Symptom control • Exacerbations • Adverse events • Mortality (Annualized exacerbation rate)

Nair et al.[21] ZONDA Phase 3 RCT of add-on therapy with steroid tapering Moderate	• Subjects aged 18 to 75 • Blood eosinophil count at least 150/µL • Medium- to high-dose ICS and LABA • Oral steroids for at least 6 months	• Benralizumab 30 mg SC every 4 wks (n = 72) • Benralizumab 30 mg SC every 8 wks (n = 73) • Placebo (n = 75) Oral steroids adjusted to lowest possible dose to control symptoms before randomization, oral steroid dose reduced by standard amount at regular intervals, continued stable doses of other controllers, SABA rescue for symptoms	At 28 weeks: • Symptom control •QoL •Exacerbations • Steroid use • Adverse events • Mortality (Percentage reduction in steroid dose with asthma control maintained)
Panettieri et al.[20] SOLANA Phase 3 RCT of add-on therapy Moderate	• Subjects aged 18 to 75 • Eosinophilic severe asthma requiring ICS/OCS and LABA • ≥ 2 exacerbations requiring OCS in prior year ACQ score ≥ 1.5	• Benralizumab 30 mg SC every 4 wks (n = 118) • Placebo (n = 115) Co-interventions NR	At 8 to 12 wks • Symptom control • Adverse events (Change in pre-bronchodilator FEV_1)
Park et al.[19] Phase 2a RCT of add-on therapy Moderate	• Subjects aged 20 to 75 • Eosinophilic asthma • Medium- to high-dose ICS and LABA • 2 to 6 exacerbations requiring systemic steroids in past year • ACQ score ≥ 1.5	• Benralizumab 20 mg SC every 4 wks first 3 doses, then every 8 wks (n = 25) • Placebo (n = 26) Continued stable doses ICS and LABA	At 52 wks • Symptom control • Exacerbations • Adverse events • Mortality (Annualized exacerbation rate)

Abbreviations. ACQ = Asthma Control Questionnaire; FEV1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroids; LABA = long-acting beta-2 agonists; OCS = oral corticosteroids; QoL = quality of life; pre-BD = pre-bronchodilator; NR = not reported; RCT = randomized controlled trial; SABA = short-acting beta-2 agonists; SC = subcutaneous; wks = weeks

Dupilumab Compared to Placebo

Four industry-sponsored, multicenter RCTS evaluated dupilumab compared to placebo.[22-25] Two RCTs were conducted in multiple countries among children and adults aged 12 years and older,[22,25] 1 RCT was conducted in multiple countries among adults aged 18 years and older,[23] and 1 RCT[24] was conducted in the United States (US) among adults aged 18 years and older. The 2 Wenzel et al. trials were phase 2 RCTs, and the LIBERTY ASTHMA VENTURE and LIBERTY ASTHMA QUEST were phase 3 trials. The dupilumab studies are summarized in **Table 4**.

Study inclusion and exclusion criteria were similar across the 4 trials.[1] All were conducted among participants who had asthma for at least 12 months that was not well controlled with ICS, or LABAs, or both, and excluded participants with chronic obstructive pulmonary disease or other lung diseases, and current smokers.[1] LIBERTY ASTHMA VENTURE and LIBERTY ASTHMA QUEST enrolled participants without respect to baseline level of eosinophils, but reported findings overall and for the subgroups of participants with baseline eosinophils less than 150, 150 to 300, and greater than 300 cells per µL.[1] Wenzel et al. 2016 enrolled

participants without regard to baseline eosinophils but defined the primary endpoint for the subgroup with baseline eosinophils greater than 300 cells per µL.[1] Wenzel et al. 2013 enrolled only participants with baseline eosinophils greater than 300 cells per µL.[1]

Symptom Control

- Data from 2 add-on efficacy RCTs (N = 2,367)[23,25] and 2 steroid-sparing RCTs (N = 314)[22,24] were pooled to evaluate symptom control. Dupilumab was more effective compared to placebo for improving symptom control as measured by difference in mean change from baseline on the ACQ (pooled estimate, -0.28; 95% CI, -0.37 to -0.19 for add-on efficacy trials at 24 weeks and pooled estimate, -0.55; 95% CI, -0.79 to -0.31 for steroid-sparing RCTs at 12 to 24 weeks); moderate QoE.[1]
- In 1 add-on efficacy RCT (N = 465)[23] dupilumab was more effective than placebo for improving symptom control as measured by the proportion of participants achieving a MCID (0.5 points) on the ACQ (RR, 1.22; 95% CI, 1.06 to 1.40); moderate QoE.[1]

Quality of Life

- In 2 add-on efficacy RCTs (N = 2,367)[23,25] dupilumab was more effective than placebo for improving quality of life as measured by difference in mean change from baseline on the AQLQ (pooled estimate, 0.23; 95% CI, 0.08 to 0.38 at 24 weeks); moderate QoE.[1] However, the pooled analysis at 24 weeks did not render a mean reduction that achieved a MCID for the AQLQ (0.5 points).[1]
- Data from 1 add-on efficacy RCT (N = 465)[23] showed dupilumab was more effective than placebo for improving quality of life as measured by proportion of participants achieving an MCID (0.5 points) on the AQLQ (RR 1.81; 95% CI, 1.28 to 2.57 for 200-mg dose; RR 1.27; 95% CI, 1.05 to 1.53 for 300-mg dose); moderate QoE.[1]

Exacerbations

- In 1 add-on efficacy RCTs (N = 465)[23] dupilumab 300 mg was more effective than placebo for reducing the annualized rate of severe exacerbations at 24 weeks (relative risk reduction 70.5; 95% CI 45.4 to 84.1), moderate QoE.[1]
- Data from 1 add-on efficacy RCT (N = 1,902)[25] demonstrated dupilumab was more effective than placebo in lowering the rate of exacerbations requiring ED visit or hospitalization (IRR 0.53; 95% CI, 0.25 to 0.82); low QoE.[1]

Corticosteroids

- 1 steroid-sparing RCT (N = 314)[22] showed dupilumab was more effective compared to placebo at reducing the use of maintenance corticosteroids as measured by 50% or greater reduction in corticosteroid dose (calculated RR 1.49; 9% CI 1.22 to 1.83), moderate QoE.[1]

Overall Adverse Effects and Serious Adverse Effects

- Data pooled from the 4 RCTs in **Table 4** (N = 2,367) revealed no significant difference between dupilumab and placebo in rates of overall AEs (pooled RR 0.99; 95% CI, 0.95 to 1.03); high QoE.[1] Data from 4 RCTs also showed no significant difference between dupilumab and placebo in SAEs (pooled RR, 1.05; 95% CI, 0.80 to 1.38); moderate QoE.[1]

Mortality

- Only 1 study reported mortality; no deaths were reported in either the dupilumab or placebo group.[1]

Table 4. Randomized Controlled Trials of Dupilumab in Patients with Asthma[1]

Trial Citation Trial Name Study Design Risk of Bias	Population	Intervention (n) Comparator (n) Co-interventions	Outcomes Assessed (Primary Designated Outcome)
Rabe et al.[22] LIBERTY ASTHMA VENTURE Phase 3 RCT of add-on therapy with steroid tapering Moderate	• Subjects aged 12 and older • Treatment with systemic glucocorticoids in prior 6 months • High-dose inhaled glucocorticoid, up to 2 controllers in prior 3 months • No minimum requirement for eosinophils but 80% had atopic medical history	• Dupilumab 300 mg SC every 2 wks, loading dose 600 mg (n = 103) • Placebo (n = 107) Glucocorticoid dose (prednisone or prednisolone) with dose reduced every 4 wks during weeks 4 to 20. Background asthma controllers at stable dose and SABA as needed.	At 24 weeks: • Symptom control • Steroid use • Adverse events • Mortality (Percentage reduction in oral glucocorticoid dose while asthma control was maintained)
Wenzel et al., 2016[23] No trial name Phase 2b trial of effectiveness of add-on therapy Moderate	• Subjects aged 18 and older • Treatment with medium- to high-dose ICS and LABA with a stable dose for 1 month or longer • ACQ-5 total score 1.5 or higher • 1 or more systemic corticosteroid burst therapy, hospital admission, or an emergency or urgent medical care visit that required treatment with systemic steroids for worsening asthma in prior year • No minimum requirement for eosinophils but primary endpoint defined based on subgroup with ≥ 300/µL	• Dupilumab 200 mg SC every 2 or 4 wks, 400-mg loading dose (n = 150) • Dupilumab 300 mg SC every 2 or 4 wks, 600-mg loading dose (n = 157) • Placebo (n = 158) High-dose ICS and LABA use in 1 of 3 approved combinations.	At 24 weeks: • Symptom control • QoL • Exacerbations • Adverse events • Mortality (Change from baseline in FEV_1 at week 12 in subpopulation of patients with baseline eosinophil count of ≥ 300/µL)
Wenzel et al, 2013[24] No trial name Phase 2a trial of add-on therapy with LABA discontinuation and steroid tapering Moderate	• Subjects aged 18 to 65 years • Asthma not well controlled with medium-dose to high-dose inhaled glucocorticoids plus LABAs • ACQ-5 ≥ 1.5 and ≤ 3.0 • Eosinophils ≥ 300/µL • At least 1 asthma exacerbation within prior 2 years resulting in	• Dupilumab 300 mg SC every 1 wk (n = 52) • Placebo (n = 52) Combination therapy with ICS and LABAs, ICS dose based on pretrial doses for 4 wks.	At 12 weeks: • Symptom control • Exacerbations • Adverse events • Mortality (Occurrence of asthma exacerbation)

	treatment with 1 or more systemic steroid or hospitalization or an emergency care visit	Discontinuation of LABA at week 4 and tapering of ICS during weeks 6 through 9.	
Castro et al.[25] LIBERTY ASTHMA QUEST Phase 3 RCT of effectiveness of add-on therapy Moderate	• Subjects aged 12 and older • Treatment with medium- to high-dose ICS plus up to 2 additional controllers • Worsening asthma in prior year that led to hospitalization • Emergency medical care, or treatment with systemic steroids for ≥3 days • ACQ score ≥ 1.5 • No minimum requirement for eosinophils but 82% had atopic medical history	• Dupilumab 200 mg SC every 2 wks, loading dose 400 mg (n = 631) • Dupilumab 300 mg SC every 2 wks, loading dose 600 mg (n = 633) • Placebo (n = 638) • High-dose ICS; continued stable dose asthma-controller medicines; LABA, long-acting muscarinic antagonists, LTRAs, and methylxanthines; SABA as necessary for symptom relief.	At 52 weeks: • Symptom control • QoL • Exacerbations • Adverse events • Mortality (Annualized rate of severe asthma exacerbations)
Abbreviations. ACQ = Asthma Control Questionnaire; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroids; LABA = long-acting beta-2 agonists; LTRA = leukotriene receptor antagonist OCS = oral corticosteroids; QoL = quality of life; pre-BD = pre-bronchodilator; NR = not reported; RCT = randomized controlled trial; SABA = short-acting beta-2 agonist; SC = subcutaneous; wk(s) = week(s)			

Mepolizumab Compared to Placebo

Three phase 3 industry-sponsored RCTs (SIRIUS,[26] MENSA,[27] and MUSCA[28]) evaluated mepolizumab compared to placebo.[1] All trials were international, multicenter studies conducted between the years 2012 and 2016. MENSA and MUSCA enrolled with participants aged 12 to 75 with eosinophilic asthma on high-dose ICS with at least 2 exacerbations requiring systemic steroids in the prior year.[27,28] SIRIUS enrolled participants aged 18 to 82 and required participants to have a 6-month history of maintenance systemic steroids in addition to treatment with high-dose ICS and another controller medication.[26] MENSA and MUSCA were designed to assess the efficacy of a 100-mg dosage of mepolizumab as add-on therapy compared to placebo without a steroid taper.[27,28] SIRIUS was designed to assess the efficacy of add-on mepolizumab (100 mg) compared to placebo during a steroid-tapering cointervention in both study groups.[26] All participants in SIRIUS continued treatment with high-dose ICS and an additional controller medication (LABA, LTRA, or theophylline) throughout the study.[26] The risk of bias of these trials was rated as moderate for extensive manufacturer involvement in study design, execution, and reporting.[1] A summary of these trials is presented in **Table 5**.

Symptom control

- Pooled data from the 2 add-on efficacy RCTs (N = 941)[27,28] showed mepolizumab was more effective than placebo in improving symptom control as measured by difference in mean change from baseline on ACQ at 24 to 32 weeks follow-up (mean difference (MD) -0.43, 95% CI, -0.59 to -0.27, P=0.001); moderate QoE.[1]

Quality of Life

- No studies reported specific measures assessing quality of life with mepolizumab administration in patients with asthma.[1]

Exacerbations

- MUSCA and MENSA both reported exacerbation outcomes at 32 and 24 weeks, respectively, but MENSA did not provide enough information to conduct a pooled analysis.[1] MUSCA showed participants allocated to mepolizumab had a significantly lower annualized exacerbation rate (IRR, 0.42; 95% CI, 0.31 to 0.56; moderate QoE) and a lower rate of exacerbations requiring an ED visit or hospitalization (IRR 0.32; 95% CI, 0.12 to 0.90; low QoE) compared to placebo.[1] MENSA also reported a lower annualized exacerbation rate among persons allocated to mepolizumab compared to placebo (0.83 vs. 1.74; calculated IRR 0.48; moderate QoE) and a lower annualized rate of exacerbations requiring an ED visit or hospitalization (0.03 vs. 0.10, 69% decrease; 95% CI, 9% to 89% decrease; low QoE).[1]

Corticosteroid use

- In 1 steroid-sparing RCT (N = 135)[28], mepolizumab was more effective compared to placebo in reduction of corticosteroid use as measured by the proportion of participants able to reduce oral steroid doses by 50% or more (54% vs. 33%; RR 1.61; 95% CI, 1.07 to 2.41); low QoE.[1]

Overall Adverse Effects

- Data pooled from the 3 RCTs in **Table 5** (N = 556) demonstrated fewer AEs occurred among participants allocated to mepolizumab versus placebo (pooled RR 0.93; 95% CI, 0.88 to 0.99); high QoE.[1]

Serious Adverse Effects

- Pooled analyses of the MENSA and MUSCA trials also observed fewer SAEs in the mepolizumab group compared to placebo (pooled RR 0.63; 95% CI, 0.41 to 0.97).[1] SIRIUS was not included in this pooled analysis because the findings introduced substantial heterogeneity for reasons that could not be explained based on study or population characteristics.[1] In SIRIUS, 1 of 69 (1.4%) people experienced SAEs in the mepolizumab group compared to 12 of 66 (18.2%) in the placebo group (calculated RR, 0.07; 95% CI, 0.01 to 0.60).[1]

Mortality

- Of the 3 studies evaluating mepolizumab, only MUSCA reported mortality; no deaths were reported in either the treatment or placebo group.[1]

Table 5. Randomized Controlled Trials of Mepolizumab in Patients with Asthma[1]

Trial Citation Trial Name Study Design Risk of Bias	Population	Intervention (n) Comparator (n) Co-interventions	Outcomes Assessed (Primary Designated Outcome)
Bel et al.[26] SIRIUS Phase 3 RCT of add-on therapy with steroid tapering Moderate	• Aged 12 to 75 • Eosinophilic asthma • Maintenance systemic steroids, high-dose ICS and controller medication (LABA, LTRA, or theophylline)	• Mepolizumab 100 mg SC every 4 wks (n = 69) • Placebo (n = 66) Oral steroids adjusted to lowest possible dose to control symptoms before randomization; oral steroid dose reduced by standard amount at regular intervals, continued stable doses of other controllers, SABA rescue for symptoms.	At 24 weeks: • Symptom control • QoL • Exacerbations • Steroid use At 32 weeks: • Adverse events • Mortality (Percentage reduction in steroid dose with asthma control maintained)

Ortega et al.[27] MENSA Phase 3 RCT of add-on therapy Moderate	• Aged 18 to 82 • Eosinophilic asthma • High-dose ICS and controller medication, at least 2 exacerbations requiring systemic steroids in prior year	• Mepolizumab 100 mg SC every 4 wks (n = 194) • Placebo (n = 191) Continued stable doses of other asthma controllers, SABA rescue for symptoms.	At 32 weeks: • Symptom control • QoL • Exacerbations At 40 weeks: • Adverse Events • Mortality (Annualized exacerbation rate)
Chupp et al.[28] MUSCA Phase 3 RCT of add-on therapy Moderate	• Aged 12 to 75 • Eosinophilic asthma • High-dose ICS and controller medication • At least 2 exacerbations requiring systemic steroids in prior year	• Mepolizumab 100 mg SC every 4 wks (n = 276) • Placebo (n = 280) Continued stable doses of other asthma controllers, SABA rescue for symptoms.	At 24 weeks: • Symptom control • QoL • Exacerbations • Adverse events • Mortality (HRQOL mean change)
Abbreviations. ACQ = Asthma Control Questionnaire; FEV_1 = forced expiratory volume in 1 second; HRQOL = health-related quality of life; ICS = inhaled corticosteroids; LABA = long-acting beta-2 agonists; LTRA = leukotriene receptor antagonists; OCS = oral corticosteroids; QoL = quality of life; pre-BD = pre-bronchodilator; NR = not reported; RCT = randomized controlled trial; SABA = short-acting beta-2 agonists; SC = subcutaneous; wk(s) = week(s)			

Reslizumab Compared to Placebo

Seven industry-sponsored studies (published in 5 articles) evaluated reslizumab compared to placebo.[29-33] Six studies were phase 3 RCTs while the Castro et al.[30] trial was a phase 2 trial. Corren et al.[33] was conducted in the US among adults aged 18 to 65, and Castro et al.[32] was conducted in the US and Canada among adults aged 18 to 75. The remaining 5 RCTs were conducted at multiple sites in multiple countries among participants aged 12 to 75 or participants aged 12 and older. The risk of bias as rated as moderate for all studies because of extensive manufacturer involvement in study design, execution, and reporting.[1] Study details are presented in **Table 6**.

Study inclusion and exclusion criteria were similar; all studies were conducted with participants who had asthma that was poorly controlled by at least a medium-dose ICS or a high-dose of ICS.[1] Six of the studies enrolled participants based on higher baseline blood eosinophils (e.g., more than 300 or 400 cells per µL).[1] Corren et al.[33] did not enroll participants based on baseline blood eosinophils, and 80% of those enrolled had levels less than 400 cells per µL. Six of the studies were add-on therapy efficacy trials that assessed 110 mg SC or 3 mg per kg IV of reslizumab every 4 weeks compared to placebo.[1] The FDA-approved dose of reslizumab is 3 mg per kg IV, and a 110-mg SC dose approximates a dose of 1 mg per kg IV for a 70-kg person.[1] One of the studies reported in Bernstein et al.[29] assessed 110 mg SC of reslizumab every 4 weeks as add on-therapy during a steroid-tapering co-intervention. This study included participants with oral corticosteroid-dependent severe asthma who required an average daily maintenance dose of oral corticosteroids (5 to 40 mg of prednisone or equivalent) during the 3 months before study entry; participants had their oral steroid doses optimized during the run-in period to the lowest possible dosage to maintain asthma control.[29]

Symptom control

- Pooled data from 5 add-on efficacy RCTs (N = 1,766)[29-33] showed reslizumab was more effective than placebo for improving symptom control as measured by difference in mean change from baseline in ACQ at 15 to 16 weeks (pooled estimate, -0.25; 95% CI, -0.33 to -0.17); moderate QoE.[1]
- Pooled data from 5 add-on efficacy RCTs (N = 1,766) [30-34] demonstrated reslizumab was more effective than placebo as measured by the proportion of participants achieving an MCID (0.5 points) on the ACQ at 15 to 52 weeks (range of pooled RRs, 1.24 to 1.28); high QoE.[1]

Quality of life

- Pooled data from 4 add-on efficacy RCTs (N = 1,632)[29,31,32] showed reslizumab was more effective over placebo for improving quality of life as measured by difference in mean change from baseline on the AQLQ at 15 to 52 weeks (range of pooled estimates, 0.24 to 0.21); moderate QoE.[1]
- Pooled data from 3 add-on efficacy RCTs (N = 1,164)[31,32] demonstrated reslizumab was more effective than placebo for improving quality of life as measured by the proportion of participants achieving an MCID (0.5 points) on the AQLQ at 16 to 52 weeks (range of pooled RRs, 1.14 to 1.35); high QoE.[1]

Exacerbations

- Pooled data from 3 add-on efficacy RCTs (N = 1,421)[29,32] showed reslizumab was more effective compared to placebo for reducing the annualized rate of exacerbations (pooled IRR, 0.53; 95% CI, 0.36 to 0.71 in add-on efficacy trials at 52 weeks; absolute rates NR); high QoE.[1]
- Pooled data from 3 add-on efficacy RCTs (N = 1,421) [30,32] demonstrated no difference between reslizumab and as measured by annualized rate of exacerbations requiring ED or hospital visit (pooled IRR, 0.73; 95% CI, 0.36 to 1.09; absolute rates NR); low QoE.[1]

Corticosteroid Use

- 1 steroid-sparing RCT (N = 177)[30] demonstrated no difference between reslizumab and placebo in reducing corticosteroid use as measured by percentage change in oral maintenance steroid dose (difference in mean percentage dose change, -17.8; 95% CI, -39.0 to 3.5); low QoE.[1]

Overall Adverse Effects and Serious Adverse Effects

- Data pooled from the 7 RCTs presented in **Table 5** (N = 2,411) showed no difference between reslizumab and placebo in overall AEs (pooled RR, 0.92; 95% CI, 0.84 to 1.00); high QoE.[1] Data pooled from 7 RCTs showed no difference between reslizumab and placebo in overall SAEs (pooled RR, 0.94; 95% CI, 0.68 to 1.31); moderate QoE.[1]

Mortality

- Six of the 7 studies reported mortality. Events were rare (2 deaths out of 2,300 total participants across studies), so estimates of treatment effect were imprecise.[11]

Table 6. Randomized Controlled Trials of Reslizumab in Patients with Asthma[1]

Trial Citation Trial Name Study Design Risk of Bias	Population	Intervention (n) Comparator (n) Co-interventions	Outcomes Assessed (Primary Designated Outcome)
Bernstein et al., 2020 (study 1)[29] No trial name Phase 3 RCT of add-on therapy Moderate	• Aged 12 and older with uncontrolled severe asthma • Eosinophils ≥ _300/µL • At least a medium dose of ICS with 1 or more additional asthma controllers	• Reslizumab 110 mg SC every 4 wks (n = 236) • Placebo (n = 232) Continued inhaled asthma controller regimen; oral corticosteroids as needed	At 32 or 52 weeks: • Symptom control • QoL • Exacerbations • Adverse events • Mortality

	• ACQ score > 1.5		(Frequency of exacerbations)
Bernstein et al., 2020 (study 2)[29] No trial name Phase 3 RCT of add-on therapy with steroid tapering Moderate	• Aged 12 and older with severe asthma • Eosinophils ≥ _300/µL • Daily maintenance oral corticosteroid • High-dose ICS plus another controller	• Reslizumab 110 mg SC every 4 wks (n = 88) • Placebo (n = 89) Continued ICS use; minimal effective oral corticosteroid dose optimized during run-in and continued for first 4 weeks of double-blind treatment, then reduced from weeks 5 to 20, maintained at lowest dose for last 4 weeks	At 24 weeks: • Symptom control • QoL • Steroid Use • Exacerbations • Adverse events • Mortality (Percentage reduction in daily oral steroid dose)
Castro et al., 2011[30] No trial name Phase 2 RCT of add-on therapy Moderate	• Aged 18 to 75 with poorly controlled asthma • Using high-dose ICS with at least 1 other agent • ACQ score > 1.5 • Induced sputum eosinophils ≥ _3%	• Reslizumab 3 mg/kg IV every 4 wks (n = 53) • Placebo (n = 53) Continued ICS use	At 15 weeks: • Symptom control • Exacerbations • Adverse events (Change in ACQ score)
Bjermer et al., 2016[31] BREATH-3 Phase 3 RCT of add-on therapy Moderate	• Aged 12 to 75 with inadequately controlled asthma • Receiving treatment with at least a medium-dose ICS • ACQ score > 1.5 • Eosinophils ≥ _400/µL	• Reslizumab 3 mg/kg IV every 4 wks (n = 106) • Placebo (n = 105) Continued long-acting bronchodilators, LTRA, or cromolyn	At 16 weeks: • Symptom control • QoL • Adverse events • Mortality (FEV1 change)
Castro et al., 2015[32] BREATH-2 Phase 3 RCT of add-on therapy Moderate	• Aged 12 to 75 with inadequately controlled asthma • Receiving treatment with at least a medium-dose ICS with or without another controller drug • ACQ score > 1.5 • Eosinophils ≥ _400/µL	• Reslizumab 3 mg/kg IV every 4 wk (n = 232) • Placebo (n = 232) Continued usual asthma treatment, including LABAs, ICS, oral corticosteroids LTRAs, and cromolyn	At 16 or 52 weeks: • Symptom control • QoL • Exacerbations • Adverse events • Mortality (Incidence and rate exacerbations)
Castro et al., 2015[32] BREATH-1 Phase 3 RCT of add-on therapy Moderate	• Aged 12 to 75 with inadequately controlled asthma • Receiving treatment with at least a medium-dose ICS with or without another controller	• Reslizumab 3 mg/kg IV every 4 wk (n = 245) • Placebo (n = 244)	At 16 or 52 weeks: • Symptom control • QoL • Exacerbations • Adverse events

	• ACQ score > 1.5 • Eosinophils ≥ _400/µL	Continued usual asthma treatment, including LABAs, ICS, oral corticosteroids, LTRAs, and cromolyn	• Mortality (Incidence and rate of exacerbations)
Corren et al., 2016[33] No trial name Phase 3 RCT of add-on therapy Moderate	• Aged 18 to 65 with inadequately controlled asthma • On at least a medium-dose ICS • ACQ score > 1.5 • Allergic asthma (20%)	• Reslizumab 3 mg/kg IV every 4 wk (n = 398) • Placebo (n = 98) Continued LABAs, LTRAs, 5-lipoxengase inhibitors, or cromolyn; rescue medications as needed	At 16 weeks: • Symptom control • Adverse events • Mortality (FEV1 change)
Abbreviations. ACQ = Asthma Control Questionnaire; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroids; IV = Intravenous; LABA = long-acting beta-2 agonists; LTRA = leukotriene receptor antagonists; OCS = oral corticosteroids; QoL = quality of life; pre-BD = pre-bronchodilator; NR = not reported; RCT = randomized controlled trial; SABA = short-acting beta-2 agonists; SC = subcutaneous; wk(s) = week(s)			

Omalizumab Compared to Placebo

Twenty-three RCTs evaluated 1 or more dosing regimens of omalizumab for management of moderate to severe asthma.[1] One RCT used a no-treatment control group, and 2 RCTs used a control group characterized as optimized asthma therapy and best standard-of-care treatment.[1] The rest of the RCTs used placebo comparators.[1] There was strong variation in QoE ratings for outcomes related to omalizumab, ranging from very low to high.[1] Eight studies were evaluated as high risk for bias for various methodological issues, including lack of intervention masking, no description of randomization and allocation concealment or baseline differences among groups, selective outcome reporting, selection bias related to recruitment or unexplained post-randomization exclusions, deviation from intervention protocol, and high attrition.[1]

Of the 23 included studies, 15 were entirely sponsored by the manufacturer, 6 had partial funding from the manufacturer, 1 reported no sponsor information, and 1 was funded by a government agency.[1] All but 1 study were multicenter trials.[1] Six studies were phase 4 post marketing RCTs, 4 studies were phase 3 RCTs, 1 study was a phase 2 RCT, and trial phase was not reported in the remaining 12 studies.[1] Six studies were conducted in the US, and the rest were conducted in other countries or globally in multiple countries.[1] Eight studies were conducted among adults, 4 were conducted among participants under age 18 years, and the rest were conducted among participants aged 12 and older.[1]

Study entry criteria were reasonably similar across studies. In addition to requiring moderate to severe asthma, most required participants to have allergic asthma, including evidence of a positive skin prick or radioallergosorbent test (RAST) for 1 or more environmental allergens.[1] Most studies were designed to evaluate the efficacy of omalizumab as add-on therapy to existing asthma controller medications and rescue medications as needed. However, 6 RCTs were designed to evaluate the efficacy of omalizumab as add-on therapy during a steroid-tapering cointervention.[1] The specific details for the 23 RCTs are summarized in the DERP report.[1]

Symptom control

- Pooled data from 3 add-on efficacy RCTs in adults (N = 721) showed omalizumab was more effective over placebo in symptom control as measured by difference in mean change in days with asthma symptoms over 1 to 2 weeks (pooled estimate, -0.48 days; 95% CI, -0.74 to -0.23); high QoE.[1]
- Pooled data from 2 add-on efficacy RCTs in adults (N = 691) revealed omalizumab had a larger improvement in mean change from baseline on the ACT compared with placebo (pooled estimate, 0.52; 95% CI, 0.14 to 0.91); low QoE.[1]

Quality of Life

Across the add-on efficacy trials and the trials that included steroid-tapering, omalizumab was more effective than placebo for improving quality of life as measured by the AQLQ mean change from baseline (moderate QoE), and MCID response on the AQLQ (high QoE).[1] However, in 2 trials of add-on efficacy with steroid-tapering in children ages 6 to 11, there was no difference in change in quality of life as measured by the Pediatric AQLQ (PAQLQ) mean change from baseline in 1 trial (low QoE) and no difference as measured by a large MID response in the PAQLQ in another trial (low QoE).[1]

- Four add-on efficacy RCTs (N = 1,791) showed omalizumab was more effective compared to placebo in improving quality of life as measured by the AQLQ mean change from baseline, but data suitable for pooling was not available.[1] Across the 4 RCTs, the mean improvement from baseline in the AQLQ score was larger for participants allocated to omalizumab compared to placebo or control (range, 0.29 to 1.19); moderate QoE.[1]
- Three add-on efficacy RCTs (N = 1,662) demonstrated omalizumab was more effective compared to placebo as measured by the proportion of respondents achieving an MCID (0.5 points) on the AQLQ at 28 to 46 weeks (pooled RRs range, 1.15; 95% CI 1.07 to 1.23); high QoE.[1]
- One steroid-sparing RCT (N = 627) showed no difference between omalizumab versus placebo as measured by difference in mean change from baseline on the PAQLQ: 0.04; 95% CI, NR; low QoE.[1]
- In 1 steroid-sparing RCT (N = 334), there was no difference in proportion of participants achieving a large MCID (1.5 points) on the PAQLQ (RRs, 1.45 to 1.67 across trial phases but measures of variance did not exclude a null effect); low QoE.[1]

Exacerbations

- Data from 12 add-on efficacy RCTs (N = 3,646) and 4 steroid-sparing RCTs (N = 2,032) revealed omalizumab was more effective over placebo for reducing the incidence of exacerbations in adults (pooled RR, 0.71; 95% CI, 0.61 to 0.82 for add-on efficacy trials; range of pooled RRs, 0.55 to 0.67 across trial phases in steroid-sparing RCTs; absolute rates NR); high QoE.[1]
- Data from 3 add-on efficacy RCTs (N = 1,309) showed omalizumab was more effective compared with placebo in adults as measured by the incidence or rate of exacerbations requiring ED or hospital visits (RRs and IRRs range from 0.23 to 0.66 across studies; absolute rates NR); moderate QoE.[1]

Corticosteroid Use

- Three steroid-sparing RCTs in adults (N = 1,317) showed omalizumab was more effective than placebo as measured by the proportion of participants who reduced their maintenance inhaled steroid dose by 50% or more (pooled RRs range, 1.39 to 1.40 across various steroid trial phases: steroid-stable, steroid-reduction, and extension); high QoE.[1]

Overall Adverse Effects

- 17 RCTs (N = 23,751) reported no difference in AEs at 16 to 60 weeks of follow-up between omalizumab versus placebo (pooled RR, 1.00; 95% CI, 0.97 to 1.03); high QoE.[1]

Serious Adverse Effects

- 16 RCTs (N = 23,561) reported fewer SAEs occurred among participants allocated to omalizumab versus placebo (pooled RR, 0.76; 95% CI, 0.59 to 0.99); moderate QoE.[1]

Mortality

- Nine studies reported mortality outcomes. In 5 studies, no deaths occurred in either study group, and in the remaining 4 studies, deaths were very rare (6 deaths out of 1,738 participants).[5]

New Indications

Mepolizumab

Mepolizumab received FDA-approval in September 2020 for an expanded indication for the treatment of adult and pediatric patients aged 12 years and older with HES with a duration of 6 months or greater without an identifiable non-hematologic secondary cause.[2] The recommended mepolizumab dose for HES is 300 mg (given as 3 separate 100 mg injections) SC every 4 weeks, this dose is significantly higher than recommended dosing in asthma patients.[2] Hypereosinophilic syndromes are rare disorders marked by the overproduction of eosinophils which cause damage to multiple organs.[34] Hypereosinophilia has generally been defined as a peripheral blood eosinophil count greater than 1,500 cells per µL.[35] The goal of treatment for patients with HES is the long-term reduction of blood and tissue eosinophil levels to reverse and prevent end-organ damage.[34] With the exception of patients with imatinib-sensitive HES variants (including those associated with the FIP1-like-1-platelet-derived growth factor receptor alpha fusion gene [FIP1L1-PDGFRA]), the standard of care consists of glucocorticoids and cytotoxic/immunosuppressive therapy.[34] First-line therapy for all patients with the FIP1L1-PDGFRA mutation is the tyrosine kinase inhibitor, imatinib mesylate.[35]

The evidence for the expanded mepolizumab indication was provided from 1 trial conducted in 104 adult and adolescent patients aged 12 years and older with FIP1L1-PDGFRA-negative HES.[34] Patients with non-hematologic secondary HES or FIP1L1-PDGFRA kinase-positive HES were excluded from the trial.[34] The study was a randomized, placebo-controlled, multicenter, 32-week treatment trial. Patients entering the trial had experienced at least 2 HES flares within the previous 12 months and a blood eosinophil count of 1,000 cells per µL or higher during screening.[34] Historical HES flares for the trial entry criteria were defined as HES-related worsening of clinical symptoms or blood eosinophil counts requiring an escalation in therapy.[34] Patients must have been on stable HES therapy for the 4 weeks prior to randomization. HES therapy could include chronic or episodic oral corticosteroids (OCS), immunosuppressive, or cytotoxic therapy.[34] Subjects received 300 mg of mepolizumab or placebo subcutaneously once every 4 weeks.

The primary endpoint was the proportion of patients who experienced a flare during the 32-week treatment period.[34] An HES flare was defined as worsening of clinical signs and symptoms of HES or increasing eosinophils (on at least 2 occasions), resulting in the need to increase oral steroids or increase/add immunosuppressive HES therapy.[34] Over the 32-week treatment period, the incidence of HES flare over the treatment period was 56% (30 of 54 subjects) for the placebo group and 28% (15 of 54 subjects) for the group treated with mepolizumab (OR 0.28; 95% CI 0.12 to 0.64; P = 0.002).[34] Difference was observed between mepolizumab and placebo arms in the time to first HES flare. The risk of first HES flare over the treatment period was 66% lower for patients treated with mepolizumab compared with placebo (26.3% vs. 52.7%; hazard ratio: 0.34; 95 % CI 0.18, 0.67, P = 0.002).[34] Similar proportions of patients in the mepolizumab and placebo groups experienced on-treatment adverse events (89 versus 87 percent, respectively).[34] The higher mepolizumab dose was well tolerated in the HES trial and no additional mepolizumab adverse reactions were identified than those reported in the severe asthma trials.[2]

Omalizumab

In November 2020, omalizumab received FDA-approval for treatment of nasal polyps in adult patients 18 years of age and older with inadequate response to nasal corticosteroids, as add on maintenance treatment.[3] The recommended dose for treatment of nasal polyps is 75 mg to 600 mg SC every 2 or 4 weeks based on serum total IgE level and by body weight.[3] In contrast, the asthma dosing for omalizumab is 75 mg to 375 mg SC every 2 or 4 weeks based on serum total IgE level and body weight.[3]

The safety and efficacy of omalizumab was evaluated in two, randomized, multicenter, double- blind, placebo-controlled clinical trials that enrolled patients with nasal polyps with inadequate response to nasal corticosteroids (POLYP 1, n=138; POLYP 2, n=127).[36] Patients received weight-based omalizumab or placebo SC every 2 or 4 weeks, for 24 weeks followed by a 4-week follow-up period.[36] All patients received background nasal mometasone therapy during both the treatment period and during a 5-week run-in period.[36] Prior to randomization, patients were required to have evidence of bilateral polyps as determined by a

nasal polyp score (NPS) of at least 5 with NPS greater than or equal to 2 in each nostril, despite use of nasal mometasone during the run-in period. NPS was measured via endoscopy and given a score of 0 to 4 per nostril for a total NPS range of 0 to 8. Scores were based on the following criteria: 0= no polyps; 1=small polyps in the middle meatus not reaching below the inferior border of the middle turbinate; 2=polyps reaching below the lower border of the middle turbinate; 3=large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate; and 4=large polyps causing complete obstruction of the inferior nasal cavity.[36] Patients were furthermore required to have a weekly average of nasal congestion score (NCS) greater than 1 prior to randomization, indicating moderate to severe congestion despite use of nasal mometasone.[36] Nasal congestion was measured by a daily assessment on a 0 to 3 point severity scale (0=none, 1=mild, 2=moderate, 3=severe).[36] The co-primary endpoints in POLYP 1 and 2 were NPS and average daily NCS at Week 24.[36] In POLYP 1 and POLYP 2, the mean changes from baseline at week 24 for omalizumab versus placebo were as follows: NPS, –1.08 versus 0.06 (Difference:-1.14; 95% CI -1.59 to -0.69; P <0.0001) and –0.90 versus –0.31 (Difference: -0.59; 95% CI -1.05 to -0.12; P=0.014); NCS, –0.89 versus –0.35 (Difference: -0.55; 95% CI -0.84 to -0.25; P = 0.0004) and –0.70 versus –0.20 (Difference: -0.50; 95% CI -0.80 to -0.19; P = 0.0017).[36] In both trials, patients who received omalizumab had a statistically significant greater improvement from baseline at Week 24 in NPS and weekly average NCS, than patients who received placebo.[3]

New Formulations

Omalizuamb

In April 2021, the FDA approved a prefilled syringe for self-administration of omalizumab for treatment of persistent asthma in patients 6 years and older, chronic idiopathic urticaria in patients 12 years and older, and nasal polyps in patients 18 years and older.[3] Chronic idiopathic urticaria is not funded by HERC, therefore, claims for this indication are not covered for Oregon Medicaid FFS patients.

Mepolizumab

In September 2019, the FDA approved a new prefilled syringe for self-administration of mepolizumab for treatment of severe eosinophilic asthma in patients 6 years and older, adult patients with eosinophilic granulomatosis with polyangiitis (EGPA), and adults and adolescents aged 12 years and older with HES without an identifiable non-hematologic secondary cause.[2]

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
montelukast sodium	MONTELUKAST SODIUM	ORAL	TAB CHEW	Y
montelukast sodium	SINGULAIR	ORAL	TAB CHEW	Y
montelukast sodium	MONTELUKAST SODIUM	ORAL	TABLET	Y
montelukast sodium	SINGULAIR	ORAL	TABLET	Y
benralizumab	FASENRA PEN	SUB-Q	AUTO INJCT	N
benralizumab	FASENRA	SUB-Q	SYRINGE	N
mepolizumab	NUCALA	SUB-Q	AUTO INJCT	N
mepolizumab	NUCALA	SUB-Q	SYRINGE	N
mepolizumab	NUCALA	SUB-Q	VIAL	N
montelukast sodium	MONTELUKAST SODIUM	ORAL	GRAN PACK	N
montelukast sodium	SINGULAIR	ORAL	GRAN PACK	N
omalizumab	XOLAIR	SUB-Q	SYRINGE	N
omalizumab	XOLAIR	SUB-Q	VIAL	N
reslizumab	CINQAIR	INTRAVEN	VIAL	N
roflumilast	DALIRESP	ORAL	TABLET	N
zafirlukast	ACCOLATE	ORAL	TABLET	N
zafirlukast	ZAFIRLUKAST	ORAL	TABLET	N
zileuton	ZYFLO	ORAL	TABLET	N
zileuton	ZILEUTON ER	ORAL	TBMP 12HR	N

Appendix 2: Medline Search Strategy

Databases(s): Ovid MEDLINE (R) 1996 to May Week 2, 2021
Ovid MEDLINE(R) In-Process and In-Data-Review Citations 1946 to May Week 12, 2021

1.	benralizuamb.mp	303
2.	Mepolizumab.mp	704
3.	Omalizumab	1769
4.	Reslizumab.mp	234
5.	Dupilumab.mp	812
6.	1 or 2 or 3 or 4 or 5	3272
7.	limit 6 to (english language and humans and yr=”2020-current”)	351
8.	limit to clinical trial or guideline, or meta-analysis or practice guideline or systematic review	37

Monoclonal Antibodies for Severe Asthma

Goal(s):

- Restrict use of monoclonal antibodies to patients with severe asthma requiring chronic systemic corticosteroid use or with history of asthma exacerbations in the past year that required an Emergency Department visit or hospitalization.
- Restrict use for conditions not funded by the OHP (e.g., chronic urticaria).

Length of Authorization:

- Up to 12 months

Requires PA: Pharmacy and physician-administered claims for the following drugs:

- Biologic drugs with indications for asthma (see **Table 2** below)

~~Omalizumab~~
~~Mepolizumab~~
~~Reslizumab~~
~~Benralizumab~~
~~Dupilumab~~
~~This PA does not apply to dupilumab, which is subject to separate clinical PA criteria.~~

Covered Alternatives:

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

Table 1. Maximum Adult Doses for Inhaled Corticosteroids.

High Dose Corticosteroids:	**Maximum Dose**
Qvar (beclomethasone)	320 mcg BID
Pulmicort Flexhaler (budesonide)	720 mcg BID
Alvesco (ciclesonide)	320 mcg BID
Aerospan (flunisolide)	320 mcg BID
Arnuity Ellipta (fluticasone furoate)	200 mcg daily
Flovent HFA (fluticasone propionate)	880 mcg BID
Flovent Diskus (fluticasone propionate)	1000 mcg BID
Asmanex Twisthaler (mometasone)	440 mcg BID
Asmanex HFA (mometasone)	400 mcg BID
High Dose Corticosteroid / Long-acting Beta-agonists	**Maximum Dose**
Symbicort (budesonide/formoterol)	320/9 mcg BID
Advair Diskus (fluticasone/salmeterol)	500/50 mcg BID
Advair HFA (fluticasone/salmeterol)	460/42 mcg BID

Wixela Inhub (fluticasone/salmeterol)	500/50 mcg BID
Airduo RespiClick (fluticasone/salmeterol)	464/28 mcg BID
Breo Ellipta (fluticasone/vilanterol)	200/25 mcg daily
Dulera (mometasone/formoterol)	400/10 mcg BID

Table 2. FDA-approved indications and ages

Drug	Eosinophilic Asthma	Moderate to Severe Persistent Asthma	Hypereosinophilic Syndrome (HES)	Eosinophilic Granulomatosis with Polyangiitis (EGPA)	Chronic Rhinosinusitis with Nasal Polyposis (CRSwNP)	Atopic Dermatitis (AD)
Dupilumab	≥12 years (or with oral corticosteroid dependent asthma)				≥18 years	≥6 years
Benralizumab	≥12 years					
Reslizumab	≥18 years					
Mepolizumab	≥6 years		≥ 12 years	≥18 years		
Omalizumab		≥6 years			≥18 years	

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is the diagnosis an OHP-funded diagnosis? Note: chronic idiopathic urticaria is not an OHP-funded condition	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.

Approval Criteria		
~~3.~~4. Is the request for an FDA-~~-~~approved indication and age (**Table 2**)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Does the patient have a concurrent prescription for EpiPen® or equivalent so they are prepared to manage delayed anaphylaxis if it occurs after monoclonal antibody therapy?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is the diagnosis Severe Atopic Dermatitis (AD)?	**Yes:** Go to #7	**No:** Go to #9
7. Is the medication being prescribed by or in consultation with a dermatologist or a provider who specializes in care of atopic dermatitis?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Does the patient have a documented contraindication or failed trial of the following treatments: • Moderate to high potency topical corticosteroid (e.g., clobetasol, desoximetasone, desonide, mometasone, betamethasone, halobetasol, fluticasone, or fluocinonide) AND • Topical calcineurin inhibitor (tacrolimus, pimecrolimus) or topical phosphodiesterase (PDE)-4 inhibitor (crisaborole) AND • Oral immunomodulator therapy (cyclosporine, methotrexate, azathioprine, mycophenolate mofetil, or oral corticosteroids)?	**Yes**: Document drug and dates trialed and intolerances (if applicable): 1._____(dates) 2._____(dates) 3._____(dates) Approve for length of treatment; maximum 6 months.	**No**: Pass to RPh. Deny; medical appropriateness

Approval Criteria		
~~4.~~9. Is the ~~claim~~ request for ~~mepolizumab in an adult patient diagnosed with~~ eosinophilic granulomatosis with polyangiitis (EGPA, formerly known as Churg-Strauss Syndrome) for at least 6 months that is refractory to at least 4 weeks of oral corticosteroid therapy (equivalent to oral prednisone or prednisolone 7.5 to 50 mg per day)?	**Yes:** Approve for 12 months. Mepolizumab dose: 300 mg (3 x 100mg syringes) every 4 weeks	**No:** Go to #10
10. Is the ~~claim~~request for ~~mepolizumab for~~ the treatment of ~~an adult or pediatric~~ patient ~~aged 12 years and older~~ with hypereosinophilic syndrome (HES) with a duration of 6 months or greater without an identifiable non-hematologic secondary cause?	**Yes:** Approve for 12 months. Mepolizumab dose: 300 mg (3 x 100mg syringes) every 4 weeks ~~x 1 year~~	**No:** Go to #11
11. Is the ~~claim for omalizumab for the~~request for treatment of ~~an adult with~~ nasal polyps?	**Yes:** Go to # 12	**No:** Go to #14
12. Is the prescriber an otolaryngologist, or allergist who specializes in treatment of chronic rhinosinusitis with nasal polyps?	**Yes:** Go to # 13	**No:** Pass to RPh. Deny; medical appropriateness
13. Has the patient failed medical therapy with intranasal corticosteroids (2 or more courses administered for 12 to 26 weeks[1])?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness
~~5.~~14. Is the prescriber a pulmonologist or an allergist who specializes in management of severe asthma?	**Yes:** Go to #15	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
~~6.~~15. Has the patient required at least 1 hospitalization or ≥ 2 ED visits in the past 12 months while receiving a maximally-dosed inhaled corticosteroid (Table 1) AND 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, tiotropium)?	**Yes:** Go to #16 Document number of hospitalizations or ED visits in past 12 months: _____. This is the baseline value to compare to in renewal criteria.	**No:** Pass to RPh. Deny; medical appropriateness.
~~7.~~16. Has the patient been adherent to current asthma therapy in the past 12 months?	**Yes:** Go to #17	**No:** Pass to RPh. Deny; medical appropriateness.
~~8.~~17. Is the patient currently receiving another monoclonal antibody for asthma (e.g., dupilumab, omalizumab, mepolizumab, benralizumab or reslizumab)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #18
~~9.~~18. If the claim is for omalizumab, can the prescriber provide documentation of allergic IgE-mediated asthma diagnosis, confirmed by a positive skin test or in vitro reactivity to perennial allergen?	**Yes:** Approve once every 2-4 weeks for up to 12 months. Document test and result:_____	**No:** Go to #19

Approval Criteria		
~~10.~~19. If the ~~claim~~ request is for ~~mepolizumab, benralizumab or reslizumab~~asthma with an eosinophilic phenotype, can the prescriber provide documentation of severe eosinophilic asthma, confirmed by blood eosinophil count ≥300 cells/µL in the past 12 months?	**Yes:** Approve once every 4 to 8 weeks for up to 12 months. Note: Initial benralizumab dose is 30 mg every 4 weeks x 3 doses followed by 30 mg every 8 weeks Document eosinophil count (date):_____	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the request to renew ~~mepolizumab~~ therapy for ~~,~~ EGPA, nasal polyps, or HES?	**Yes:** Go to #2	**No:** Go to #3
2. Have the patient's symptoms improved with ~~mepolizumab~~ therapy?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is the request to renew therapy for atopic dermatitis?	**Yes:** Go to #4	**No:** Go to #5

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

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P&T Review: *8/21 (DM); 10/20 (KS),7/19 (DM); 7/18; 7/16*
Implementation: *8/19/19, 8/15/18, 8/16*

Dupilumab -RETIRE

Goal(s):

- Promote use that is consistent with national clinical practice guidelines and medical evidence.

Length of Authorization:

- 6 months

Requires PA:

- Dupilumab (Dupixent)

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD 10 code.	
2. Is the diagnosis an OHP funded diagnosis?	**Yes:** Go to #3	**No:** Pass to RPh. Deny, not funded by the OHP.
3. Is this a request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4
4. Is the product requested preferred?	**Yes:** Approve for length of treatment; maximum 1 year.	**No:** Go to #5

Approval Criteria		
5. Will the prescriber consider a change to a preferred product? **Message:** Preferred products are evidence-based reviewed for comparative effectiveness & safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform provider of preferred alternatives. Approve for length of treatment; maximum 1 year.	**No**: Go to # 6
6. Is the medication being prescribed by or in consultation with a dermatologist, otolaryngologist, or allergist who specializes in management of severe asthma?	**Yes:** Go to # 7	**No:** Pass to RPh. Deny; medical appropriateness
7. What is the age of the patient? • Dupilumab injection is FDA approved for patients 12 years of age and older for management of atopic dermatitis and moderate-to-severe asthma.	**Age 11 years or younger**: Pass to RPh. Deny; medical appropriateness.	**Ages 12 years and older:** Go to #8
8. Is the diagnosis Moderate/Severe Atopic Dermatitis (AD)?	**Yes:** Go to #9	**No:** Go to #10

Approval Criteria		
9. Does the patient have a documented contraindication or failed trial of the following treatments: • Moderate to high potency topical corticosteroid (e.g., clobetasol, desoximetasone, desonide, mometasone, betamethasone, halobetasol, fluticasone, or fluocinonide) AND • Topical calcineurin inhibitor (tacrolimus, pimecrolimus) or topical phosphodiesterase (PDE)-4 inhibitor (crisaborole) AND • Oral immunomodulator therapy (cyclosporine, methotrexate, azathioprine, mycophenolate mofetil, or oral corticosteroids)?	**Yes**: Document drug and dates trialed and intolerances (if applicable): 1._____(dates) 2._____(dates) 3._____(dates) Approve for length of treatment; maximum 6 months.	**No**: Pass to RPh. Deny; medical appropriateness
10. Is the claim for moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma?	**Yes:** Go to #11	**No:** Go to # 14
11. Is the patient currently receiving another monoclonal antibody for asthma (e.g., omalizumab, mepolizumab, benralizumab or reslizumab)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #12
12. Has the patient required at least 1 hospitalization or ≥ 2 ED visits in the past 12 months while receiving a maximally-dosed inhaled corticosteroid (Table 1) AND 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, theophylline)?	**Yes:** Go to #13 Document number of hospitalizations or ED visits in past 12 months: _____. This is the baseline value to compare to in renewal criteria.	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
13. Has the patient been adherent to current asthma therapy in the past 12 months?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness.
14. Does the patient have chronic rhinosinusitis with nasal polyposis and is the patient an adult? *Use of dupilumab in chronic rhinosinusitis with nasal polyposis is only approved in adults.	**Yes:** Go to # 15	**No:** Pass to RPh. Deny; medical appropriateness.
15. Has the patient failed medical therapy with intranasal corticosteroids (2 or more courses administered for 12 to 26 weeks[1])?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness

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

Renewal Criteria		
3. Is the request to renew dupilumab for moderate to severe asthma?	**Yes:** Go to # 4	**No:** Go to # 6
4. Is the patient currently taking an inhaled corticosteroid and 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, theophylline)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Has the patient reduced their systemic corticosteroid dose by ≥50% compared to baseline?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh. Deny; medical appropriateness.
6. Have the patient's symptoms of chronic rhinosinusitis with polyposis improved?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness.

P&T/DUR Review: 9/21 (DM); 9/19 (DM); 7/19 (DM)

Implementation: TBD: 8/19/19

1. Chong LY, Head K, Hopkins C, Philpott C, Burton MJ, Schilder AG. Different types of intranasal steroids for chronic rhinosinusitis. *Cochrane Database Syst Rev.* 2016; 4:Cd011993.

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Drug Class Literature Scan: Phosphate Binders

Date of Review: August 2021

Date of Last Review: March 2016
Literature Search: 1/01/2016 – 05/19/2021

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

Conclusions:

- Since the 2016 phosphate binder class update, 2 systematic reviews[1,2] and 1 guideline[3] have been published.
- The goal of a 2018 Cochrane systematic review was to update a previous review focused on an assessment of the benefits and harms of phosphate binders for preventing and treating bone disease in people with chronic kidney disease (CKD).[1] One hundred four studies met inclusion criteria involving 13,744 adults.[1] Sixty-nine new studies were added to the 2018 update.[1] In studies of adults with CKD treated with dialysis, sevelamer may lower all-cause death compared to calcium-based phosphate binders (i.e., calcium carbonate, calcium acetate; low Quality of Evidence [QoE]).[1] Not unexpectedly, calcium-based phosphate binders incurred substantially increased risks of hypercalcemia.[1] No clinically important benefits of any phosphate binder on bone fracture were identified.[1] When compared to placebo, sevelamer may incur nausea while lanthanum may lead to nausea and constipation, and iron-based binders may lead to diarrhea or constipation.[1] Sevelamer and lanthanum may have similar risks of nausea, vomiting or constipation compared with calcium-based binders.[1]
- The Canadian Agency for Drugs and Technologies in Health (CADTH) published an assessment of the clinical effectiveness of sevelamer compared to calcium-based phosphate binders) for the treatment of adults with CKD.[2] Eleven publications were reviewed for the report. Clinical effectiveness outcomes included serum phosphate levels, serum calcium levels, hypercalcemia, achievement of serum phosphate target levels and vascular calcification. Overall, moderate QoE suggests that sevelamer is more effective at reducing serum calcium levels and lowering the risk of hypercalcemia in patients with CKD compared to calcium-based phosphate binders, but may be less effective at lowering serum phosphate levels.[2] The evidence on the impact of sevelamer on the risk of adverse events (e.g., all-cause mortality rates and cardiovascular mortality rates) remains inconclusive.[2]
- The Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline for diagnosis, evaluation, prevention and treatment of CKD mineral and bone disorders was updated in 2017.[3] The KDIGO 2017 guidelines suggest there is insufficient evidence for efficacy and safety of phosphate binders among patients with CKD Grade 3a through 5 not receiving dialysis.[3] Phosphate binders should be limited to patients with progressive or persistent hyperphosphatemia and not to prevent hyperphosphatemia.[3] Not all phosphate binders are interchangeable, and excess exposure to calcium, as with calcium-based binders, may be harmful across all grades of CKD.[3] There remains some uncertainty about the evidence that calcium-free agents are superior to calcium-based agents for prevention of adverse clinical outcomes in adults.[3] The 2017 KDIGO update suggests restricting the dose of calcium-based phosphate binders, and tolerance of mild or asymptomatic hypocalcemia, in order to avoid exogenous calcium loading.[3]

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Recommendations:

- Current evidence does not support changes to the Preferred Drug List (PDL).
- Remove Prior Authorization (PA) requirement for preferred non-calcium products from phosphate binder criteria.
- Review costs in executive session.

Summary of Prior Reviews and Current Policy

The phosphate binder drug class was last reviewed by the Pharmacy and Therapeutics (P & T) Committee at the March 2016 meeting. There is no evidence that one phosphate binder is more effective or safer than another; however, there is more long-term evidence with sevelamer and lanthanum compared to sucroferric oxyhydroxide and ferric citrate. The preferred phosphate binders on the PDL include calcium acetate and sevelamer HCl tablets. Non-preferred agents are listed in **Appendix 1.** The final recommendations from the 2016 P & T review were to continue to prefer at least one calcium-based phosphate binder and one non-calcium-based phosphate binder on the PDL. No changes to the current Prior Authorization (PA) criteria were recommended at that time. (**Appendix 6**). In the first quarter of 20201, approximately 60% of Fee-For-Service (FFS) phosphate binder claims were for calcium acetate formulations and 40% of FFS utilization was due to nonpreferred agents, primarily sevelamer.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

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

This literature scan focuses on phosphate binders approved in the United States (US) to manage hyperphosphatemia associated with CKD.

New Systematic Reviews:

- **Cochrane: Phosphate Binders For Preventing And Treating Chronic Kidney Disease-Mineral And Bone Disorder**

The 2018 Cochrane systematic review updates a 2011 Cochrane review of the benefits and harms of phosphate binders for preventing and treating bone disease in people with CKD.[1] The literature search was conducted through July 2018. Relevant endpoints included musculoskeletal and cardiovascular morbidity, myocardial infarction, stroke, hospitalization, vascular calcification, bone fracture, and death.[1] Surrogate endpoints included serum phosphate levels, parathyroid hormone (PTH) levels and fibroblast growth factor-23 (FGF23) levels.[1] Recent KDIGO guidelines recommend that investigations contributing to the understanding of the usefulness of FGF23 as a complementary marker for treatment indications (e.g., phosphate-lowering therapies to halt CKD progression) should be undertaken.[3] One hundred four studies met inclusion criteria involving 13,744 adults.[1] Sixty-nine new studies were added to the 2018 update.[1] Adults with CKD enrolled in the trials had Grades 2, 3, 4 and 5 (GFR 15 to 90 mL/min) and Stage 5D (requiring dialysis) CKD.[1] Studies of phosphate binders in children with CKD or patients with a kidney transplant were excluded and have been reviewed in separate Cochrane reviews.[4,5]

Comparisons between sevelamer, lanthanum, iron, calcium, magnesium, and aluminum hydroxide were included.[1] Studies comparing phosphate binders (sevelamer, lanthanum, calcium, and ferric citrate) to placebo or usual care without binder administration were largely limited to adult patients with CKD not requiring dialysis (15/25 studies involving 1467 participants).[1] Head-to-head studies were predominantly conducted among patients with CKD treated with dialysis (74/81 studies involving 10,364 participants).[1] The duration of study follow-up ranged from 8 weeks to 36 months (median 3.7 months).[1] The sample size ranged from 8 to 2103 participants (median=69).[1] The mean age of study participants ranged between 42 and 68 years.[1]

Of the 104 trials, random sequence generation and allocation concealment were low risk of bias in 25 and 15 studies, respectively.[1] Twenty-seven studies reported low risk for performance and detection bias.[1] Thirty-one studies were at low risk of attrition bias and 69 studies were at low risk of selective reporting bias.[1] Key methodological limitations included attrition from follow-up due to events that may have been related to the clinical outcomes of interest, differences between treatment groups, or relatively larger proportions of randomized participants.[1] A summary of trials for drugs FDA-approved in the US discussed in the 2018 Cochrane review is presented in **Table 1**.

Table 1. Summary of Trials Evaluating Safety and Efficacy of Phosphate Binders in People with Chronic Kidney Disease[1]

Comparison	Number of Studies	Population Size and Description	Study Duration and Follow-Up	Comments
Phosphate Binder versus Placebo or Usual Care				
Sevelamer vs. Placebo or Usual Care	7	N = 667 CKD not requiring dialysis	2 to 24 mos Median: 3 mos	6 studies involved adults with CKD not requiring dialysis. Evidence certainty for CKD patients treated with dialysis is very low.
Lanthanum vs. Placebo or Usual Care	7	N = 515 CKD not requiring dialysis	3 to 12 mos Median: 3 mos	6 studies involved adults with CKD not requiring dialysis. Evidence certainty for CKD patients treated with dialysis is very low.
Ferric Citrate vs. Placebo or Usual Care	3	N = 422 CKD not requiring dialysis or adults with CKD treated with HD	1.8 to 3 mos Median: 2.75 mos	2 studies involved adults with CKD not requiring dialysis. 1 study involved adults with CKD treated with HD. Evidence certainty for CKD patients treated with dialysis is very low.
Calcium Carbonate vs. Placebo	4	N = 278 CKD not requiring dialysis or adults with CKD treated with HD	3 to 9 mos Median: 7 mos	3 studies involved adults with CKD not requiring dialysis. 1 study involved adults with CKD treated with HD. Evidence certainty for CKD patients treated with dialysis is very low.
Non-calcium phosphate binder versus calcium phosphate binder				
Sevelamer vs. Calcium Carbonate Or Calcium Acetate	30	N = 5424 CKD treated with HD or PD	1.8 to 24 mos Median: 5.5 mos	24 studies involved adults with CKD treated with HD. 1 study involved adults with CKD treated with PD. Evidence certainty for CKD patients not requiring dialysis is very low.
Lanthanum vs. Calcium Carbonate Or Calcium Acetate	14	N = 1690 CKD treated with HD or PD	1.8 to 18 mos Median: 6 mos	9 studies involved adults with CKD treated with HD. 3 studies involved adults with CKD treated with PD. Evidence certainty for CKD patients not requiring dialysis is very low.
Sevelamer Plus Calcium Carbonate vs. Calcium Carbonate	1	N = 35 CKD treated with HD	36 mos	Data from 1 study reported no differences between sevelamer and combination sevelamer plus calcium-based binders for hypercalcemia.

Sevelamer vs. Calcium Acetate Plus Magnesium	1	N = 255 CKD treated with HD	6 mos	No differences between sevelamer and combination calcium/magnesium for serum phosphate, serum calcium, and serum iPTH. Serum alkaline phosphate was reported to be lower with calcium/magnesium, and serum bicarbonate was reported to be lower with sevelamer.
Sevelamer vs. Sevelamer Plus Calcium therapy	1	N = 71 CKD treated with HD	2. 8 mos	No differences between sevelamer and combination sevelamer/calcium therapy were reported for hypercalcemia.
Magnesium vs. Calcium Carbonate	1	N = 30 CKD treated with HD	2. 8 mos	No differences between magnesium and calcium in rates of hospitalization, constipation or diarrhea were reported.
Magnesium Plus Calcium therapy vs. Calcium therapy	4	N = 157 CKD treated with HD or PD	3 to 30 mos Median: 7.5 mos	No comments, see summary discussed in the narrative below.
Aluminum Hydroxide vs. Calcium Carbonate Or Calcium Acetate	2	N = 67 CKD treated with HD	6 to 12 mos	Data from 1 study could not be extracted. Data from the other trial reported lower serum alkaline phosphate with calcium-based binders vs. aluminum hydroxide.
Non-calcium phosphate binder versus non-calcium phosphate binder				
Sevelamer vs. Lanthanum	3	N = 197 CKD treated with HD	2 to 12 mos	Data from two studies could not be extracted for meta-analysis. Data from 1 study reported no differences between sevelamer and lanthanum for myocardial infarction, stroke, fracture, pruritis, nausea, vomiting, abdominal pain, constipation, diarrhea, abdominal bloating, and hypercalcemia.
Sevelamer vs. Iron Based Binders	4	N = 1704 CKD treated with HD or PD	3 to 6 mos Median: 3 mos	3 studies involved adults with CKD treated with HD or PD. Evidence certainty for CKD patients not requiring dialysis is very low.
Sevelamer vs. Aluminum Hydroxide	1	N = 30 CKD treated with PD	16 mos	No differences reported between sevelamer and aluminum for nausea, constipation, serum phosphate, serum calcium, and serum intact PTH.
Sevelamer vs. Magnesium Carbonate	1	N = 40 CKD treated with HD	3 mos	Serum phosphate was lower with magnesium; serum calcium was lower with sevelamer and there was no difference between the groups for serum intact PTH.
Lanthanum Carbonate vs. Ferric Citrate	1	N = 18 CKD treated with HD	3 mos	Data could not be extracted from this study.
Phosphate Binder Comparisons				
Sevelamer Hydrochloride vs. Sevelamer Carbonate	1	N = 296 CKD treated with HD	5.5 to 12 mos	No differences reported for death, nausea, vomiting, constipation, and diarrhea between the 2 groups.
Calcium Carbonate vs. Calcium Acetate	4	N = 209 CKD treated with HD	2 to 12 mos Median: 3 mos	No comments, see summary discussed in the narrative below
Abbreviations: CKD = chronic kidney disease; HD = hemodialysis; mos = months; PD = peritoneal dialysis; PTH = parathyroid hormone; vs. = versus				

Sevelamer versus Placebo or Usual Care

None of the 7 studies evaluating sevelamer with placebo or usual care was designed to evaluate death or cardiovascular events.[1] Evidence was generally restricted to people with CKD not requiring dialysis.[1] In 3 studies, deaths were reported as reasons for withdrawal from study follow-up.[1] A single study reported 1 or more deaths during a median of 10 months.[1] Sevelamer had uncertain effects on all causes of death (3 studies, n=248: Risk Ratio [RR] 2.16, 95% CI 0.20 to 22.84; very low QoE).[1] No studies reported whether deaths due to cardiovascular events occurred.[1] Two studies each reported 1 participant experiencing a myocardial infarction, while a third study reported zero events on a studies registry web site.[1] Whether sevelamer prevents myocardial infarction is uncertain due to very low QoE (RR 1.00, 95% CI 0.11 to 9.35).[1] A single study reported one stroke event in the sevelamer group.[1] One study reported no difference in the number of patients requiring hospitalization during follow-up.[1] One study reported two bone fracture events in the control group and one participant experienced pruritus in the control group.[1]

In the assessment of biochemical responses to therapy, the mean serum phosphate level was 0.28 mg/dL lower (range: 0.39 to 0.94 mg/dL) with sevelamer compared to placebo at a median of 3 months, in an analysis of 5 studies characterized by heterogeneity (I^2 = 95%; leading to very low QoE).[1] Compared with placebo or usual care, sevelamer did not have clinically important effects on serum calcium (Mean Difference [MD] 0.03 mg/dL, 95% CI -0.08 to 0.14).[1] The impact of sevelamer treatment on hypercalcemia was uncertain as a single study reported 1 event in each study group.[1] Sevelamer had uncertain effects on the serum intact PTH (iPTH), serum alkaline phosphatase, serum bicarbonate, estimated glomerular filtration rate (eGFR), and bone mineral density measured at the hip or spine.[1] Serum FGF23 levels were not reported in a format that was extractable for meta-analysis.[1]

With respect to adverse events, nausea was reported in 3 studies (370 participants) in a meta-analysis marked by heterogeneity (I^2 = 71%).[1] Sevelamer had uncertain risks of nausea (RR 1.27, 95% CI 0.07 to 22.42), vomiting (2 studies, n=165: RR 2.09, 95% CI 0.26 to 16.57), abdominal pain (3 studies, n=370: RR 0.38, 95% CI 0.13 to 1.14), and diarrhea (2 studies, n=165: RR 2.02, 95% CI 0.13 to 31.62) based on very low QoE.[1] Compared with placebo or usual care, sevelamer may lead to an increased risk of constipation (4 studies, n=430: RR 6.92, 95% CI 2.24 to 21.38; low QoE).[1]

Lanthanum versus Placebo or Usual Care

None of the 7 studies comparing lanthanum to placebo or usual care were designed to measure death or cardiovascular events.[1] Evidence was generally restricted to people with CKD not requiring dialysis.[1] Three studies reported death as either a reason for study withdrawal or as an adverse event.[1] Compared with placebo or usual care, it was uncertain whether lanthanum made any difference to the risk of death (3 studies, n=214: RR 1.63, 95% CI 0.07 to 37.12; very low QoE) after a median study follow-up of 3 months.[1] No study reported cardiovascular deaths. Three studies reported myocardial infarction as an adverse treatment event, with only two events reported in the lanthanum group.[1] Lanthanum had uncertain effects on myocardial infarction (3 studies, n=239; RR 1.61, 95% CI 0.17 to 14.97). There were no reports of stroke, no difference in hospitalization events, and no difference in fractures.[1]

After a median of 3 months, the average serum phosphate level was 0.48 mg/dL lower (range: 0.05 to 0.90 mg/dL) with lanthanum compared to placebo; low QoE).[1] Lanthanum did not lead to clinically important effects on serum calcium (MD 0.03 mg/dL, 95% CI -0.18 to 0.23 mg/dL) and the risks of hypercalcemia were uncertain in one study.[1] The effects of sevelamer were uncertain for the outcomes of serum iPTH, eGFR, bone mineral density at the lumbar spine measured as a Z-score, and serum FGF23 levels.[1] Single studies reported no difference in treatment effects of lanthanum on end stage renal disease (ESRD), coronary artery calcification, or vascular calcification.[1]

Adverse events were measured over a median of 2 to 3 months.[1] Lanthanum may have led to nausea (4 studies, n=383: RR 3.72, 95% CI 1.36 to 10.18; low QoE) and probably leads to increased risk of constipation (4 studies, n=383: RR 2.98, 95% CI 1.21 to 7.30; moderate QoE).[1] Lanthanum had uncertain risks of abdominal pain (2 studies, n=120: RR 0.23, 95% CI 0.03 to 1.96; low QoE) and diarrhea (3 studies, n=261: RR 0.68, 95% CI 0.13 to 3.68; low QoE).[1]

Iron versus Placebo or Usual Care

In the 3 studies that compared iron-based binders with placebo or usual care, one study included dialysis patients and 2 studies included patients with CKD not requiring dialysis.[1] The studies were not designed to measure the effects of treatment on death or cardiovascular events.[1] Death (all causes) was reported in 2 studies.[1] At 2.75 to 3 months, iron-based binders had uncertain effects on all-cause death (2 studies, n=239: RR 0.52, 95% CI 0.06 to 4.65; very low QoE).[1] Cardiovascular death, myocardial infarction, and stroke were not reported.[1] No differences were reported in the risks of fracture, pruritus, or nausea.[1] Outcome data for vascular calcification and bone-related outcomes could not be extracted for analysis.[1]

Iron-based binders lowered serum phosphate levels (3 studies, n=301: MD -1.33 mg/dL, 95% CI -2.25 to -0.41 mg/dL; low QoE) in an analysis possessing substantial between-study heterogeneity (I^2=91%).[1] Iron-based binder therapy may be associated with higher serum calcium levels (3 studies, n=301: MD 0.21 mg/dL; 95% CI 0.09 to 0.33mg/dL).[1] Studies reported uncertain effects on serum alkaline phosphatase and serum bicarbonate.[1] Iron-based binders had uncertain effects on eGFR (2 studies, n=239: MD -0.67 mL/min, 95% CI -2.97 to 1.64).[1] Outcome data for serum FGF23 levels could not be extracted for analysis.[1] Iron-based binders had clinically uncertain risks for abdominal pain (2 studies, n=332: RR 1.20, 95% CI 0.34 to 4.27), while probably increasing the risk of constipation (3 studies, n=422: RR 2.66, 95% CI 1.15 to 6.12; moderate QoE) and diarrhea (3 studies, n=422: RR 2.81, 95% CI 1.18 to 6.68; moderate QoE).[1]

Calcium versus Placebo or Usual Care

Evidence evaluating calcium versus placebo was generally restricted to people with CKD not requiring dialysis.[1] Meta-analyses involved 2 studies (or 3 for biochemical endpoints).[1] As a result, evidence certainty was either low, very low, or absent.[1] No study was designed to assess death or cardiovascular complications.[1] Death due to cardiovascular events was not reported in any study.[1] It is uncertain whether calcium-based phosphate binders make any difference to the risk of myocardial infarction (2 studies, n=147: RR 1.36, 95% CI 0.09 to 21.71).[1] One study reported two fractures in the placebo group.[1] Risk of pruritis from calcium-based phosphate binders was uncertain (2 studies, n=197: RR 1.19, 95% CI 0.29 to 4.81).[1]

Based on very low QoE, calcium-based phosphate binders had uncertain effects on serum phosphate (3 studies, n=151: MD- 0.18 mg/dL, 95% CI -1.30 to 0.95 mg/dL) and serum calcium (3 studies, n=151: MD 0.33 mg/dL, 95% CI -0.26 to 0.92) and heterogeneity (I^2 = 85%).[1] Hypercalcemia was reported as an adverse event after 3 months of treatment in two studies and 9 months of treatment in the third study.[1] Calcium-based binders may increase the risk of hypercalcemia (3 studies, n=215: RR 7.28, 95% CI 1.64 to 32.29; low QoE).[1] There was no uniform definition of hypercalcemia across the 3 studies. Calcium-based binders had uncertain effects on serum iPTH (2 studies, n=133: MD -80.15 pg/mL, 95% CI -305.46 to 145.16 pg/mL) and alkaline phosphatase (2 studies, n=78: MD 34.86 units/L, 95% CI -21.47 to 91.20).[1] Calcium binders may lead to a small reduction in serum bicarbonate (2 studies n=138: MD -1.85 mEq/L, 95% CI -3.12 to -0.59).[1] One study reported no differences between calcium and placebo in eGFR.[1] Outcome data for serum FGF23 levels could not be extracted for analysis.[1]

In low- or very low-certainty evidence, calcium-based binders had uncertain risks on adverse events, including nausea (2 studies, n=197: RR 0.58, 95% CI 0.15 to 2.18), abdominal pain (2 studies, n=197: RR 0.66, 95% CI 0.13 to 3.34), constipation (2 studies, n=197: RR 2.44, 95% CI 0.32 to 18.42), and diarrhea (2 studies, n=197: RR 0.94, 95% CI 0.39 to 2.28).[1] One trial reported one vomiting event in the placebo group.[1] Another trial reported no differences between the two groups in coronary artery calcium score at 2 years.[1]

Sevelamer versus Calcium

Studies comparing sevelamer with calcium were primarily conducted in participants with CKD treated with dialysis (25 of 30 studies).[1] Death (all causes) was reported in 16 studies.[1] Of these, deaths were reported in 8 studies.[1] In 4 studies, all-cause or cause-specific death was a pre-specified primary or secondary outcome.[1] In low certainty evidence downgraded for study limitations and evidence of heterogeneity (I^2 = 78%), sevelamer may reduce all causes of death compared with calcium-based phosphate binders (16 studies, n=4266: RR 0.53, 95% CI 0.30 to 0.91).[1] Based on very low QoE, it was uncertain whether sevelamer had any effect on cardiovascular death (6 studies, n=2904: RR 0.45, 95% CI 0.11 to 1.77), with statistical heterogeneity (I^2 = 73%) found.[1] Myocardial infarction (2 studies, n=177: RR 1.02, 95%CI 0.11 to 9.59) and stroke (2 studies, n=102: RR 3.00, 95% CI 0.32 to 27.90) were reported for a single patient in each of 2 studies leading to very imprecise risk estimates.[1] Two studies reported hospitalization, with the evidence dominated by a single study with a large number of reported events in both groups (2 studies, n=242: RR 0.78, 95% CI 0.56 to 1.08).[1] One study reported no differences in fracture events between the two groups.[1]

Based on very low QoE with statistical heterogeneity (I^2 = 49%), sevelamer may result in less hypercalcemia compared with calcium-based binders (19 studies, n=4084: RR 0.30, 95% CI 0.20 to 0.43).[1] There was no evidence that the coronary artery calcium score at 12 or 24 months was different for sevelamer versus calcium-based binders (4 studies, n=517: MD -24.89, 95% CI -75.66 to 25.88).[1] In 23 studies involving 4360 participants, the mean serum phosphate at end of treatment was similar between treatment groups (MD 0.06 mg/dL, 95% CI -0.11 to 0.23 mg/dL; very low QoE), although there was statistical heterogeneity (I^2 = 78%) between the studies.[1] Sevelamer may reduce serum calcium compared with a calcium-based binder (22 studies, n=4313: MD -0.38 mg/dL, 95% CI -0.54 to -0.21 mg/dL, in an analysis showing statistical heterogeneity (I^2 = 92%).[1] Sevelamer was possibly associated with increased serum iPTH levels (16 studies, n=1420: MD 44.24 pg/mL, 95% CI 10.93 to 77.55).[1] It is unclear if calcium-based treatment decreases serum alkaline phosphatase compared to placebo (7 studies, n=611: MD -17.64 units/L, 95% CI -0.16 to 35.43). although the confidence interval included the possibility of no difference.[1] Sevelamer may result in lower serum bicarbonate levels (7 studies, n=695: MD -1.57 mEq/L, 95% CI -2.15 to -1.00).[1] One study reported no difference in eGFR between the groups at the end of treatment and another trial reported no differences between the groups for serum FGF23.[1]

Based on low QoE involving studies with a median follow-up of 5.5 months, sevelamer may have similar risks of nausea compared with calcium (4 studies, n=365: RR 0.98, 95% CI 0.56 to 1.71).[1] Based on 2 studies in low certainty evidence, there was no clinical difference in the risk of vomiting between sevelamer and calcium (2 studies, n=263: RR 0.95, 95% CI 0.54 to 1.69).[1] There was no evidence of important differences in treatments for the risk of abdominal pain (4 studies, n=363: RR 1.77, 95% CI 0.68 to 4.63), constipation (6 studies, n=2652: RR 1.35, 95% CI 0.71 to 2.57), diarrhea (3 studies, n=315: RR 0.98, 95%CI 0.55 to 1.75), or abdominal bloating (2 studies, n=112: RR 4.85, 95% CI 0.87 to 27.03).[1]

Lanthanum versus Calcium

Nearly all of the studies evaluated lanthanum versus calcium in patients with CKD treated with peritoneal dialysis or hemodialysis (12 of 14 studies).[1] None of the studies were designed to evaluate treatment effects on death or cardiovascular endpoints.[1] Death (all causes) was reported in 6 studies.[1] Of these, zero events were reported in 2 studies, and 7 events were reported among the remaining 4 studies at between 6 and 18 months of therapy.[1] Based on low QoE, the effect of lanthanum on all-cause death was uncertain (6 studies, n=5050: RR 0.76, 95% CI 0.18 to 3.11).[1] Endpoints for cardiovascular death, myocardial infarction, and stroke were not reported in any of the studies.[1] Based on 2 studies, there was no evidence lanthanum affected hospitalization rates (2 studies, n=88: RR 0.80, 95% CI 0.34 to 1.93). One study reported no differences between lanthanum and calcium for fracture and pruritus.[1] Another trial reported no difference between the two treatments on coronary artery calcium score.[1]

Based on very low QoE with statistical heterogeneity (I^2 = 59%), lanthanum may result in less hypercalcemia compared with calcium-based binders (8 studies, n=1347: RR 0.16, 95% CI 0.06 to 0.43).[1] Lanthanum and calcium-based binders had similar effects on serum phosphate (9 studies, n=400: MD -0.02 mg/dL, 95% CI -0.45 to 0.41), in an analysis with statistical heterogeneity (I^2 = 76%).[1] It is uncertain if serum calcium is impacted differently between lanthanum and calcium-based phosphate binders (8 studies, n=350: MD -0.28 mg/dL , 95% CI -0.59 to 0.02 mg/dL), in an analysis with statistical heterogeneity (I^2 = 81%).[1] No evidence of differences in end of treatment serum PTH (8 studies, n=597: MD 33.78 pg/mL, 95% CI -9.03 to 76.60 pg/mL; low QoE) or serum alkaline phosphatase (3 studies, n=856: MD 20.03 units/L, 95% CI -3.69 to 43.75; low QoE) were found between the two groups.[1] One trial reported a higher eGFR at the end of treatment with lanthanum.[1] Lanthanum had uncertain effects on serum FGF23 levels compared with calcium-based binders (2 studies, n=116: SMD -0.85, 95% CI -2.33 to 0.63).[1]

Evidence for treatment adverse effects was graded as low- or very low quality.[1] Lanthanum may lead to nausea (5 studies, n=1191: RR 1.65, 95% CI 0.95 to 2.89), although the estimate included the possibility of no difference.[1] Lanthanum had uncertain effects on vomiting (2 studies, n=1058: RR 3.88, 95% CI 0.48 to 31.74) with statistical heterogeneity in the analysis (I^2 = 77%).[1] There was no evidence of different effects for lanthanum and calcium on abdominal pain (2 studies, n=137: RR 0.24, 95% CI 0.03 to 1.94), constipation (5 studies, n=1213: RR 0.79, 95% CI 0.50 to 1.26), or diarrhea (2 studies, n=858: RR 2.44, 95% CI 0.34 to 17.35).[1] One trial reported no differences in abdominal bloating between the 2 groups.[1]

Magnesium plus Calcium versus Calcium

Combined magnesium and calcium-based binders were compared with calcium monotherapy in 4 studies.[1] The studies were not designed to evaluate death or cardiovascular endpoints.[1] One study reported no difference between the two groups for death as a reason for study withdrawal.[1] The effects of magnesium plus calcium compared with calcium alone on serum phosphate levels (2 studies, n=109: MD -1.26 mg/dL, 95% CI -3.52 to 1.00 mg/dL) and serum calcium levels (2 studies, n=109: MD -0.92 mg/dL, 95% CI -2.39 to 0.55 mg/dL) were uncertain with statistical heterogeneity (I^2 = 96%).[1]

Sevelamer versus Iron

Sevelamer was compared with iron-based binders in 4 studies that reported outcomes during 3 to 6 months of follow-up.[1] In 3 of the 4 studies, participants were treated with hemodialysis or peritoneal dialysis.[1] The studies were not designed to evaluate death or cardiovascular endpoints.[1] Deaths were reported as a reason for study withdrawal or as an adverse event in 2 studies.[1] Based on very low QoE, sevelamer had uncertain effects on the risk of death (all causes) (4 studies, n=1683: RR 1.07, 95% CI 0.38 to 2.98).[1] One trial reported no differences between the groups for the risk of cardiovascular death, myocardial infarction, and fractures.[1]

Based on two studies, whether sevelamer had different effects on serum phosphate levels compared with iron-based binders was uncertain in an analysis within statistical heterogeneity (2 studies, n=417: MD 0.19 mg/dL, 95% CI -0.06 to 0.43 mg/dL I^2 = 28%).[1] Sevelamer may slightly decrease serum calcium (2 studies, n=417: MD-0.16mg/dL, 95% CI -0.29 to -0.04 mg/dL compared with iron.[1] One study reported serum bicarbonate levels were lower in the sevelamer group.[1]

Compared with iron-based binders, the risk of nausea (2 studies, n=1257: RR 3.86, 95% CI 0.33 to 44.86, I^2 = 68%), abdominal pain (2 studies, n=431: RR 0.42, 95% CI 0.02 to 9.01, I^2 = 79%), constipation (4 studies, n=1699: RR 4.96, 95% CI 1.96 to 12.55, I^2 = 71%), and diarrhea (4 studies, n=1699: RR 0.28, 95% CI 0.15 to 0.54, I^2 = 51%) versus sevelamer was uncertain.[1]

Calcium Acetate versus Calcium Carbonate

Data for the comparison of calcium acetate compared with calcium carbonate were reported in 4 studies.[1] The studies were not designed to evaluate death or cardiovascular endpoints.[1] It was uncertain whether calcium acetate prevents death because the QoE was very low (2 studies, n=74: RR 1.13, 95% CI 0.07 to 17.30). Calcium acetate may lower the risk of hypercalcemia compared with calcium carbonate (2 studies, n=92: RR 0.66, 95% CI 0.45 to 0.97).[1] Calcium acetate may make little or no difference to serum phosphate levels (3 studies, n=98: MD -0.24 mg/dL, 95% CI -0.74 to 0.26 mg/dL, serum calcium (3 studies, n=98: MD -0.21 mg/dL, 95% CI -0.45 to 0.04 mg/dL), or serum alkaline phosphatase (2 studies, 35 participants: MD 1.77 units/L, 95% CI -8.80 to 12.35).[1] One study reported no difference in serum iPTH.[1] Meta-analyses of reported adverse events could not be conducted for treatment comparison.[1]

Conclusions

A key limitation in the evidence is the lack of standardization of outcome reporting in the available studies.[1] As a result, many outcomes, such as cardiovascular events, hospitalization, pruritis, calciphylaxis, and fracture were reported in few studies.[1] Despite over one hundred studies eligible for this review, only three were designed to examine nonfatal cardiovascular events and all-cause and cardiovascular death as primary or important secondary outcomes.[1] Currently, the evidence for effects of phosphate binders on cardiovascular events and cardiovascular death is uncertain due to a paucity of data.[1] In studies of adults with CKD treated with dialysis, sevelamer may lower death (all causes) compared to calcium-based binders (low QoE).[1] Head-to-head studies of sevelamer, lanthanum, iron, and other non-calcium phosphate binders were extremely limited.[1] The present Cochrane review update is consistent with existing systematic reviews demonstrating there is little or no evidence for beneficial treatment effects on cardiovascular death for non-calcium versus calcium-based binders, a marked reduction in risks of hypercalcemia with non-calcium binders, and variable hazards of gastrointestinal adverse effects with specific agents.[1]

- **Canadian Agency for Drugs and Technologies: Sevelamer for the Treatment of Patients with Chronic Kidney Disease**

In September 2016 CADTH published an assessment of the clinical effectiveness of sevelamer for the treatment of adults with CKD.[2] The study population included patients requiring dialysis and those in pre-dialysis stages. The literature search was conducted through August 2016. Studies that compared sevelamer with calcium-based phosphate binders were the focus of the report. Five systematic reviews and 1 RCT met inclusion criteria and were evaluated as moderate QoE.[2] Clinical effectiveness outcomes included serum phosphate levels, serum calcium levels, hypercalcemia, achievement of serum phosphate target levels and vascular calcification. Safety outcomes included all-cause mortality, cardiovascular mortality, and adverse gastrointestinal events (i.e., nausea, constipation, diarrhea).[2]

Overall, the evidence suggests that sevelamer is more effective at reducing serum calcium levels and lowering the risk of hypercalcemia in patients with CKD compared to calcium-based phosphate binders, but may be less effective at lowering serum phosphate levels.[2] The evidence on the impact of sevelamer on calcification, and the risk of adverse events (e.g., all-cause mortality rates and cardiovascular mortality rates) remains inconclusive.[2] Sevelamer increases the risk of diarrhea, constipation, abdominal bloating, and combined gastrointestinal events.[2] The trends are statistically significant for constipation, and combined gastrointestinal events. One important limitation of the report is the heterogeneity across the body of evidence.[2]

After review, 10 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[6-15]

New Guidelines:
High Quality Guidelines:

Kidney Disease: Improving Global Outcomes
The 2017 KDIGO clinical practice guideline update focuses on diagnosis, evaluation, prevention and treatment of CKD mineral and bone disorders (MBD).[3] The utility of calcium-free phosphate binders in reducing clinical events in CKD, balanced against their cost and potential harms has been controversial due insufficient and conflicting evidence.[1] The 2003 National Kidney Foundation Kidney Disease Outcomes Quality Initiatives (NKF-KDOQI) recommended calcium-based binders for control of hyperphosphatasemia in CKD stages 3a and 4 (GFR 30 to 59 mL/min/1.73 m2 and 15 to 29 mL/min/1.73 m2, respectively), and both calcium-based and calcium- and aluminum-free binders in CKD stages 5 and 5D (GFR < 15 mL/min/1.73 m2 and dialysis).[16] The KDIGO guidelines of 2009 recommended restricting the use of calcium-based binders in people with persistent or recurrent hypercalcemia or arterial calcification, or both, and that phosphate binders might be used in patients with CKD Grade 3a through 5 and on dialysis to achieve improvements in serum phosphate levels toward the normal range.[17]

Development of the 2017 KDIGO guideline update followed an explicit process of evidence review and appraisal published through February 2017.[3] Treatment approaches and guideline recommendations are based on systematic review of relevant trials. Appraisal of the quality of the evidence and the strength of recommendations followed the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach.[3] The work group was comprised of individuals with expertise in adult and pediatric nephrology, bone disease, cardiology, and nutrition.[3] An open public review of the draft 2017 guideline update was permitted, and all feedback received was reviewed and considered by the international work group before finalizing the guideline document for publication.[3]

The KDIGO work group concluded there is insufficient evidence for efficacy and safety of phosphate binders among patients with CKD Grade 3a through 5 not on dialysis.[3] Use of phosphate binders should be limited to patients with progressive or persistent hyperphosphatemia and not to prevent hyperphosphatemia.[3] For patients with CKD Grade 3a through 5, elevated phosphate levels should be lowered toward the normal range rather than normalized, while avoiding hypercalcemia for adult patients.[3] Most studies showed increasing risk of all-cause mortality with increasing levels of serum phosphate in a consistent and direct fashion, with moderate risk of bias and low quality of evidence.[3] Trial data demonstrating that treatments that lower serum phosphate improve patient-centered outcomes are still lacking, and therefore the strength of this recommendation remains weak.[3]

Not all phosphate binders are interchangeable, and excess exposure to calcium, as calcium-based binders, may be harmful across all CKD categories.[3] There continues to be some uncertainty about the evidence that calcium-free agents are differ from calcium-based agents for prevention of adverse clinical outcomes in adults.[3] The 2017 KDIGO update suggests restricting the dose of calcium-based phosphate binders and stresses tolerance of mild and asymptomatic hypocalcemia, in order to avoid exogenous calcium loading.[3] This is a more conservative approach compared to previously published guidance.[3]

The 2017 KDIGO guideline summary statements regarding treatment of bone and mineral disease in CKD patients include:

- In patients with CKD G3a–G5D, treatments of CKD-MBD should be based on serial assessments of phosphate, calcium, and PTH levels, considered together (Not Graded).[3]
- In patients with CKD G3a–G5D, it is suggested to lower elevated phosphate levels toward the normal range (2C: low QoE).[3]
- In adult patients with CKD G3a–G5D, it is suggested to avoid hypercalcemia (2C: low QoE).
- In children with CKD G3a–G5D, it is suggested to maintain serum calcium in the age-appropriate normal range (2C: low QoE).[3]

- In patients with CKD G3a-G5D, decisions about phosphate-lowering treatment should be based on progressively or persistently elevated serum phosphate (Not Graded).[3]
- In adult patients with CKD G3a–G5D receiving phosphate-lowering treatment, it is suggested to restrict the dose of calcium-based phosphate binders (2B: moderate QoE).
- In children with CKD G3a–G5D, it is reasonable to base the choice of phosphate-lowering treatment on serum calcium levels (Not Graded).[3]
- In patients with CKD G3a-G5D, it is recommended to avoid the long-term use of aluminum-containing phosphate binders and, in patients with CKD G5D, avoiding dialysate aluminum contamination to prevent aluminum intoxication (1C: low QoE).[3]

New Indications:
As of November 2017, an expanded indication for AURYXIA (ferric citrate) tablets for treatment of iron deficiency anemia in adults with CKD not on dialysis received FDA approval.[18] The starting dose for ferric iron 210 mg (equivalent to 1 gm ferric citrate) is 1 tablet 3 times a day with meals up to a maximum of 12 tablets daily.[18] In a trial of patients with CKD not on dialysis, patients required an average of 5 tablets per day to increase hemoglobin (Hgb) levels.[18] In contrast, the initial dosing for hyperphosphatemia in people with CKD is 2 tablets 3 times a day with meals, up to a maximum of 12 tablets daily.[18]

The expanded indication for ferric citrate is based on results of a 16-week, double-blind, placebo-controlled RCT, followed by an 8-week open-label safety extension period.[19] All patients received ferric citrate in the 8-week safety extension period. Patients not on dialysis with eGFR less than 60 mL/min/1.73 m^2, who were intolerant of, or had an inadequate therapeutic response to, oral iron supplements, with Hgb between 9.0 g/dL and 11.5 g/dL, serum ferritin less than or equal to 200 ng/mL and transferrin saturation less than or equal to 25% were enrolled in the study.[19] Patients were randomized to treatment with either ferric citrate (n=117) or placebo (n=115).[19] Dosing with ferric citrate or placebo was initiated at 3 tablets per day with meals. Dose titration could occur at weeks 4, 8 and 12 during the randomized period, and at weeks 18 and 20 during the safety extension period based on Hgb response. Use of oral or intravenous iron, or erythropoiesis stimulating agents was not permitted during the study.[19] The mean age of the patients was 65 years (range 26 to 93); 63% were female, 69% Caucasian, 30% were African American and <2% were other races.[19]

The main efficacy outcome measure was the proportion of subjects achieving an increase in Hgb of 1.0 g/dL or greater at any time point between baseline and the end of the 16-week randomized period.[20] During the 16-week randomized period 52.1% (n=61) of patients in the ferric citrate arm and 19.1% (n=22) of patients in the placebo arm had a mean change in hemoglobin from baseline of 1.0 g/dL (difference was noted as statistically significant).[19] Rates of serious adverse events were similar in the ferric citrate (12.0%) and placebo groups (11.2%).[19] Gastrointestinal disorders were the most common adverse events, with diarrhea reported in 24 (20.5%) and 19 (16.4%) and constipation in 22 (18.8%) and 15 (12.9%) patients treated with ferric citrate and placebo, respectively.[19]

New FDA Safety Alerts:

Table 2. Description of New FDA Safety Alerts[21]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Sevelamer carbonate	RENAGEL, RENVELA	May 2020	Warnings and Precautions	Patients with dysphagia, swallowing disorders, severe gastrointestinal (GI) motility disorders, including severe constipation, or major GI tract surgery were not included in the

				sevelamer clinical studies. Cases of bowel obstruction, bleeding gastrointestinal ulcers, colitis, ulceration, necrosis, and perforation have been reported with sevelamer use. Inflammatory disorders may resolve upon sevelamer discontinuation. Treatment with sevelamer should be re-evaluated in patients who develop severe gastrointestinal symptoms.

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
calcium acetate	CALCIUM ACETATE	ORAL	CAPSULE	Y
calcium acetate	CALCIUM ACETATE	ORAL	TABLET	Y
calcium acetate	ACETICAL 170	ORAL	TABLET	Y
calcium acetate	CALPHRON	ORAL	TABLET	Y
sevelamer HCl	RENAGEL	ORAL	TABLET	Y
sevelamer HCl	SEVELAMER HCL	ORAL	TABLET	Y
calcium acetate	PHOSLYRA	ORAL	SOLUTION	N
calcium acetate	CALCIUM ACETATE	ORAL	TABLET	N
calcium carb/mag carb/folic ac	MAGNEBIND 400 RX	ORAL	TABLET	N
calcium carbonate/mag carb	MAGNEBIND 300	ORAL	TABLET	N
ferric citrate	AURYXIA	ORAL	TABLET	N
lanthanum carbonate	FOSRENOL	ORAL	POWD PACK	N
lanthanum carbonate	FOSRENOL	ORAL	TAB CHEW	N
lanthanum carbonate	LANTHANUM CARBONATE	ORAL	TAB CHEW	N
sevelamer carbonate	RENVELA	ORAL	POWD PACK	N
sevelamer carbonate	SEVELAMER CARBONATE	ORAL	POWD PACK	N
sevelamer carbonate	RENVELA	ORAL	TABLET	N
sevelamer carbonate	SEVELAMER CARBONATE	ORAL	TABLET	N
sucroferric oxyhydroxide	VELPHORO	ORAL	TAB CHEW	N

Appendix 2: New Comparative Clinical Trials

A total of 75 citations were manually reviewed from the initial literature search. After further review, 74 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining trial is summarized in the table below. The full abstract is included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

<table>
<tr><th>Study</th><th>Comparison</th><th>Population</th><th>Primary Outcome</th><th>Results</th></tr>
<tr>
<td>Ogata H, et al.[22]

MC, OL, RCT

Median follow-up: 3.16 years</td>
<td>Lanthanum carbonate 750 to 1500 mg per day
N=1,063

Vs.

Calcium carbonate 1500 to 3000 mg per day
N=1,072

Medications titrated to achieve serum phosphate levels between 3.5 mg/dL and 6.0 mg/dL</td>
<td>Long term HD patients with at least 1 risk factor for vascular calcification (age >65 years, post-menopause, diabetes mellitus)

N=2,309</td>
<td>Composite CV event: CV death, nonfatal MI, stroke, unstable angina, TIA, hospitalization for HF or ventricular arrythmia

Secondary Outcome: Overall survival rate</td>
<td>Rates of CV Events and Incidence of All Cause Death
<table>
<tr><th>Drug</th><th>CV Event Incidence Rate per 100 person years</th><th>Significance</th></tr>
<tr><td>Lanthanum</td><td>4.8</td><td rowspan="2">Difference: 0.5 per 100 person years
HR: 1.11
95% CI: -0.57 to 1.56
P = 0.37</td></tr>
<tr><td>Calcium Carbonate</td><td>4.3</td></tr>
<tr><th>Drug</th><th>All Cause Death: Incidence Rate per 100 person years</th><th>Significance</th></tr>
<tr><td>Lanthanum</td><td>4.96</td><td rowspan="2">Difference: 0.43 per 100 person years
HR: 1.10
95% CI: 0.88 to 1.37
P = 0.42</td></tr>
<tr><td>Calcium Carbonate</td><td>4.53</td></tr>
</table>
Among patients undergoing hemodialysis with hyperphosphatemia and at least 1 vascular calcification risk factor, treatment of hyperphosphatemia with lanthanum carbonate compared with calcium carbonate did not result in a significant difference in composite cardiovascular events.</td>
</tr>
</table>

Abbreviations: CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio; MC = multi-center; MI = myocardial infarction; OL = open label; RCT = randomized clinical trial; TIA = transient ischemic attack

Appendix 3: Abstracts of Comparative Clinical Trials

Ogata H, Fukagawa M, Hirakata H, et al. Effect of Treating Hyperphosphatemia With Lanthanum Carbonate vs Calcium Carbonate on Cardiovascular Events in Patients With Chronic Kidney Disease Undergoing Hemodialysis: The LANDMARK Randomized Clinical Trial. *Jama.* 2021;325(19):1946-1954.[22]

Among patients with hyperphosphatemia undergoing dialysis, it is unclear whether non–calcium-based phosphate binders are more effective than calcium-based binders for reducing cardiovascular events. To determine whether lanthanum carbonate reduces cardiovascular events compared with calcium carbonate in patients with hyperphosphatemia at risk of vascular calcification undergoing hemodialysis. Open-label, randomized, parallel-group clinical trial with blinded end point adjudication performed in 2374 patients with chronic kidney disease from 273 hemodialysis facilities in Japan. Eligible patients had hyperphosphatemia and 1 or more risk factors for vascular calcification (i.e., ≥65 years, postmenopausal, diabetes). Enrollment occurred from November 2011 to July 2014; follow-up ended June 2018.Patients were randomized to receive either lanthanum carbonate (n = 1154) or calcium carbonate (n = 1155) and titrated to achieve serum phosphate levels of between 3.5 mg/dL and 6.0 mg/dL. The primary outcome was a composite cardiovascular event (cardiovascular death, nonfatal myocardial infarction or stroke, unstable angina, transient ischemic attack, or hospitalization for heart failure or ventricular arrhythmia). Secondary outcomes included overall survival, secondary hyperparathyroidism-free survival, hip fracture–free survival, and adverse events. Among 2309 randomized patients (median age, 69 years; 40.5% women), 1851 (80.2%) completed the trial. After a median follow-up of 3.16 years, cardiovascular events occurred in 147 of 1063 patients in the lanthanum calcium group and 134 of 1072 patients in the calcium carbonate group (incidence rate, 4.80 vs 4.30 per 100 person-years; difference 0.50 per 100 person-years [95% CI, −0.57 to 1.56]; hazard ratio [HR], 1.11 [95%, CI, 0.88 to 1.41], P = .37). There were no significant differences in all-cause death (difference, 0.43 per 100 person-years [95% CI, −0.63 to 1.49]; HR, 1.10 [95% CI, 0.88 to 1.37]; P = .42) or hip fracture (difference, 0.10 per 100 person-years [95% CI, −0.26 to 0.47]; HR, 1.21 [95% CI, 0.62 to 2.35]; P = .58). The lanthanum carbonate group had an increased risk of cardiovascular death (difference, 0.61 per 100 person-years [95% CI, 0.02 to 1.21]; HR, 1.51 [95% CI, 1.01 to 2.27]; P = .045) and secondary hyperparathyroidism (difference, 1.34 [95% CI, 0.49 to 2.19]; HR, 1.62 [95% CI, 1.19 to 2.20]; P = .002). Adverse events occurred in 282 (25.7%) in the lanthanum carbonate group and 259 (23.4%) in the calcium carbonate groups. Among patients undergoing hemodialysis with hyperphosphatemia and at least 1 vascular calcification risk factor, treatment of hyperphosphatemia with lanthanum carbonate compared with calcium carbonate did not result in a significant difference in composite cardiovascular events. However, the event rate was low, and the findings may not apply to patients at higher risk. ClinicalTrials.gov Identifier: NCT01578200

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to May Week 3 2021, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to May 19, 2021

1	calcium acetate.mp.	372
2	Sevelamer/	657
3	Lanthanum/	2501
4	sucroferric oxyhydroxide.mp.	65
5	ferric citrate.mp.	874
6	1 or 2 or 3 or 4 or 5	4215
7	limit 6 to (english language and yr="2016 -Current" and (clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews))	75

Phosphate Binders

Goal(s):
- Promote use of preferred drugs.
- Reserve non-calcium-based phosphate binders for second-line therapy.

Length of Authorization:
- Up to 12 months

Requires PA:
- Non-preferred phosphate binders
- ~~Preferred non-calcium-based phosphate binders~~

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 #5
3. Has the patient tried or contraindicated to calcium acetate?	**Yes:** Document trial dates and/or intolerance. Go to #4	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of preferred calcium acetate product.
4. Will the prescriber consider a change to a preferred non-calcium-based phosphate binder?	**Yes:** Approve for 1 year and inform prescriber of preferred alternatives in class.	**No:** Approve for 1 year or length of prescription, whichever is less.

Approval Criteria

5. RPh only: All other indications need to be evaluated as to whether use is for an OHP-funded diagnosis.
   - If funded and clinic provides supporting literature, approve for up to 12 months.
   - If non-funded, deny; not funded by the OHP.

P&T Review: *8/21 (DM) 1/16 (AG); 11/12; 9/12; 9/10*
Implementation: *5/1/16; 2/21/13*

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Drug Class Update: Human Immunodeficiency Virus

Date of Review: August 2021

Date of Last Review: July 2015
Dates of Literature Search: 01/01/2020 - 05/24/2021

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

Purpose for Class Update:
The purpose of this review is to evaluate new comparative literature published since the previous review and define place in therapy for a new long-acting injectable agent cabotegravir/rilpivirine (CABENUVA), recently approved by the Food and Drug Administration (FDA) for the treatment of Human Immunodeficiency Virus (HIV) type-1 infection in adults who are virologically suppressed on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine (see accompanying New Drug Evaluation).

Research Questions:
1. What are the current antiretroviral drug regimens recommended in the United States (US) for treatment and prevention of HIV transmission?
2. What is the comparative effectiveness of antiretroviral agents for treatment and prevention of HIV?
3. Are certain sub-populations (based on age, gender, ethnicity, comorbidities, disease duration, or severity) in which certain agents may be beneficial or cause more harm?

Conclusions:
- This update includes a review of 2 Drug Effectiveness Review Project (DERP) reports[1,2] related to the treatment and prevention of HIV-1. These reports summarize available literature and compare and contrast various guideline recommendations in this clinical area. A review of guidelines for clinical context include recommendations applicable to pregnant individuals and children.
- There is variation amongst guidelines related to the recommended initial treatment regimens and alternative regimens in adults. Guideline methodology and quality varies significantly.[1,2] **(Table 4, Table 5)**
- Initial therapy for most patients should consist of:[1]
    - A two-drug nucleoside reverse transcriptase inhibitor backbone combined with:
    - An add-on therapy of a non-nucleoside reverse transcriptase inhibitor, integrase strand transfer inhibitor (INSTI), or boosted protease inhibitor
- Treatment with antiretroviral therapy should begin immediately, or as soon as possible after diagnosis of HIV.[1-5]
- Majority of direct comparative evidence available is in the form of non-inferiority studies **(Table 2, Table 3)**.[1]

- Pre-exposure prophylaxis (PrEP) using continuous daily emtricitabine 200mg/tenofovir disoproxil fumarate 300 mg is recommended by reviewed guidelines for high-risk individuals. Recommended alternative drug regimens of on-demand emtricitabine 200mg/tenofovir disoproxil fumarate 300 mg vs continuous daily tenofovir disoproxil fumarate 300 mg vary between guidelines for some subpopulations.[2] **(Table 6)**
- PrEP prophylaxis using continuous emtricitabine 200 mg/tenofovir alafenamide is FDA-approved for use in at-risk adults and adolescents weighing at least 35 kg to reduce the risk of HIV-1 infection from sexual acquisition, but the indication does not include individuals at risk from receptive vaginal sex.[6]
    - Emtricitabine/tenofovir alafenamide was non-inferior to emtricitabine/tenofovir disoproxil fumarate in reducing HIV acquisition in high-risk men who have sex with men and transgender women at high-risk of HIV acquisition (incident rate ratio 0.47 [95% confidence interval 0.19-1.15]-met prespecified 50% non-inferiority margin).[7]
- Dolutegravir use in individuals at risk of conception should involve informed patient decision making. Dolutegravir is considered a preferred option in combination with a nucleoside reverse transcriptase inhibitor backbone in this sub-population.[3,5]
- Recommended medication regimens for children are highly dependent on age and weight of child. Some recommendations in infants and younger children are extrapolated from studies in adults and adolescents.[4]
- Patients with hepatitis B coinfection should receive regimens with contain at least 2 agents active against hepatitis B.[1]
- Antiretroviral use may result in weight gain, particularly when initiating and changing regimens. Women, and specifically Black women, generally experience more weight gain than men. (Grade AI) This may be higher with dolutegravir or bictegravir based regimens. The quantity of weight gained varied by study; including ≥ 10% weight gain (17.4% female vs 12.2% male; 19.7% Black females vs. 12.4% non-Black females) and 4.2 kg gain in women switching to or adding an INSTI vs. 0.2 kg for women remaining on non-INSTI regimens after 2 years.[3]
- There are limitations relating to lack of generalizability of the study populations. Most participants were white males. Few studies included participants of other genders, races, and ethnicities. This may lead to underrepresentation of severe adverse effects such as HIV-associated nephropathy (HIVAN), which disproportionately affects Black individuals. Few studies reported the percentage of participants with specific HIV risk factors, including men who have sex with men (MSM), transgender individuals, and people who inject drugs. No studies focused on findings in Medicaid populations.[1]

Recommendations:
- Evidence does not support changes to Preferred Drug List (PDL) or current policy.
- Review costs in executive session

Summary of Prior Reviews and Current Policy:
- Antiretroviral class was first reviewed in 2015. At that time a preferred drug list (PDL) was created for all antiretroviral drugs and drug combinations, and all antiretroviral agents were designated as preferred.
- In the 4th quarter of 2020, there were just under 200 patients in the Oregon Health Plan (OHP) Fee for Service (FFS) population with paid claims for ARVs.

Background:

Human immunodeficiency virus is transmitted through contact with bodily fluids such as blood, semen, vaginal secretions, and breast milk. Once infected, the virus works to destroy immune system cells. Two to 4 weeks after contracting this infection, patients often have a high viral load and are very infectious, which then progresses to a chronic phase which can last for years. While still able to infect others, the viral load is generally lower than during the acute phase.

Without antiretroviral treatment, the viral load again increases and the patient will develop Acquired Immunodeficiency Syndrome (AIDS), and become susceptible to a wide range of opportunistic infections which increase morbidity and mortality.[8]

There are an estimated 1.2 million people with HIV in the United States (US), and this includes roughly 14% who do not know they are infected. HIV type-1 is far more common in the US than HIV type-2, which is less transmittable and less virulent.[9] New diagnoses fell by 7% from 2014 to 2018.[9] Men who have sex with men (MSM) is the most common mode of transmission for new cases (66.0%), followed by heterosexual contact (23.8%), people who inject drugs (PWID) (6.6%), and combination of MSM plus PWID (3.6%).[9] Vertical transmission from mother to baby is uncommon in the US. People who are Black/African American (42.2%) and Hispanic/Latino (27.0%) make up the majority of these new cases by ethnicity, with the subgroup of Black/African American gay and bisexual men being the most affected subpopulation.[9] In 2018, Oregon had 229 (6.4/100,000) newly diagnosed and 7,050 (197.9/100,000) total cases.[9] Most patients in Oregon were male (88%).[10] Prevalence among transgender patients is difficult to quantify as health care providers have only recently begun asking about gender identity. Over half (66%) of patients in Oregon with HIV have been diagnosed for more than 10 years.[10] In 2018 there were 66 pediatric patients living with HIV who had been diagnosed at or after birth.[10] Of all patients who have been diagnosed in Oregon, roughly 88% are both in care and on treatment and 77% are virally suppressed.[10]

Since the advent of antiretroviral drugs (ARVs) in the 1980's, the prognosis for those infected with HIV has changed, and HIV is now managed as a long-term, chronic condition. Due to the propensity to develop resistance, treatment with ARVs usually includes a combination of 3 drugs from at least 2 different drug classes. Select 2-drug regimens are also approved. ARV therapies consist of 7 classes: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors (INSTIs), protease inhibitors (PIs), a fusion inhibitor, a CCR5 antagonist, a CD4 Post-attachment inhibitor, and a gp120 attachment inhibitor.[3] The latter 4 are primarily used in situations of multidrug resistance or salvage therapy. A pharmacokinetic (PK) enhancer or "booster" is often given with PIs or elvitegravir, and does not count as 1 of the total 2 or 3 drugs drugs in combination.[3] Many of these agents are co-formulated to reduce pill burden and improve adherence. A full list of available agents can be seen in **Table 1**.[3] **Appendix 5** includes a reference list of 3 letter drug abbreviations used for HIV medications.

Table 1. FDA-approved antiretroviral agents[3]

Generic Name (Abbreviation) **BRAND NAME**	**Formulation**	**Fixed-Dose Combination (FDC)**	**Single Tablet Regimen (STR)**
Nucleoside Reverse Transcriptase Inhibitors			
Emtricitabine (FTC) EMTRIVA	EMTRIVA: 200-mg hard gelatin capsule 10-mg/mL oral solution	DESCOVY (TAF/FTC) TRUVADA (TDF/FTC)	ATRIPLA (EFV/TDF/FTC) BIKTARVY (BIC/TAF/FTC) COMPLERA (RPV/TDF/FTC) GENVOYA (EVG/c/TAF/FTC) ODEFSEY (RPV/TAF/FTC) STRIBILD (EVG/c/TDF/FTC) SYMTUZA (DRV/c/TAF/FTC)
Lamivudine (3TC) EPIVIR	EPIVIR: 150-mg and 300-mg tablets 10-mg/mL oral solution	CIMDUO (TDF/3TC) EPZICOM (ABC/3TC) TEMIXYS (TDF/3TC	DELSTRIGO (DOR/TDF/3TC) DOVATO (DTG/3TC) SYMFI (EFV 600 mg/TDF/3TC) SYMFI LO (EFV 400 mg/TDF/3TC)

			TRIUMEQ (DTG/ABC/3TC)
Tenofovir Alafenamide (TAF) VEMLIDY Note: VEMLIDY is available as a 25-mg tablet for the treatment of hepatitis B.	N/A	DESCOVY (TAF/FTC)	BIKTARVY (BIC/TAF/FTC) GENVOYA (EVG/c/TAF/FTC) ODEFSEY (RPV/TAF/FTC) SYMTUZA (DRV/c/TAF/FTC)
Tenofovir Disoproxil Fumarate (TDF) VIREAD	VIREAD: 150-mg, 200-mg, 250-mg, and 300-mg tablets 40 mg/g oral powder	CIMDUO (TDF/3TC) TEMIXYS (TDF/3TC) TRUVADA (TDF/FTC)	ATRIPLA (EFV/TDF/FTC) COMPLERA (RPV/TDF/FTC) DELSTRIGO (DOR/TDF/3TC) STRIBILD (EVG/c/TDF/FTC) SYMFI (EFV 600 mg/TDF/3TC) SYMFI LO (EFV 400 mg/TDF/3TC)
Non-Nucleoside Reverse Transcriptase Inhibitors			
Doravirine (DOR) PIFELTRO	PIFELTRO: 100-mg tablet		DELSTRIGO (DOR/TDF/3TC)
Efavirenz (EFV) SUSTIVA	SUSTIVA: 50-mg and 200-mg capsules 600-mg tablet		ATRIPLA (EFV/TDF/FTC) SYMFI (EFV 600 mg/TDF/3TC) SYMFI LO (EFV 400 mg/TDF/3TC)
Etravirine (ETR) INTELENCE	INTELENCE: 25-mg, 100-mg, and 200-mg tablets		
Nevirapine (NVP) VIRAMUNE or VIRAMUNE XR	VIRAMUNE: 200-mg tablet 50-mg/5-mL oral suspension VIRAMUNE XR: 400-mg tablet		
Rilpivirine (RPV) EDURANT	EDURANT: 25 mg tablet		COMPLERA (RPV/TDF/FTC) JULUCA (DTG/RPV) ODEFSEY (RPV/TAF/FTC) <u>CABENUVA (CAB plus RPV)-Intramuscular Injection rather than tablet</u>
Protease Inhibitors			
Atazanavir (ATV) REYATAZ EVOTAZ (ATV/c)	REYATAZ: 150-mg, 200-mg, and 300-mg cap-sules 50-mg oral powder/packet	EVOTAZ: ATV 300-mg/COBI 150-mg tablet	

Darunavir (DRV) PREZISTA PREZCOBIX (DRV/c)	PREZISTA: 75-mg, 150-mg, 600-mg, and 800-mg tablets 100-mg/mL oral suspension PREZCOBIX: DRV 800-mg/COBI 150-mg tablet		SYMTUZA (DRV/c/TAF/FTC)
Lopinavir/Ritonavir (LPV/r) KALETRA Note: LPV is only available as a component of an FDC tablet that also contains RTV.	KALETRA: LPV/r 200-mg/50-mg tablets LPV/r 100-mg/25-mg tablets LPV/r 400-mg/100-mg per 5 mL of oral solution. Oral solution contains 42% alcohol.		
Ritonavir (RTV) NORVIR Note: RTV is currently used at lower doses as a PK enhancer to increase the concentrations of other PIs and not as a stand-alone PI.	NORVIR: 100-mg tablet 100-mg soft gel capsule 80-mg/mL oral solution. Oral solution contains 43% alcohol. 100 mg single packet oral powder	KALETRA (LPV/r)	
Integrase Strand Transfer Inhibitors			
Bictegravir (BIC)	50 mg in combination product only		BIKTARVY (BIC/TAF/FTC)
Cabotegravir (CAB)	VOCABRIA (CAB PO): 30-mg tablet Obtain from manufacturer for oral lead-in and oral bridging during administration of CABENUVA (CAB IM/RPV IM)		CABENUVA (CAB IM and RPV IM): 400-mg/2-mL vial 600-mg/3-mL vial
Dolutegravir (DTG) TIVICAY	TIVICAY: 10 mg, 25 mg, and 50 mg tablets 5 mg soluble tablet		DOVATO (DTG/3TC) JULUCA (DTG/RPV) TRIUMEQ (DTG/ABC/3TC)
Elvitegravir (EVG)	150 mg in combination products only		GENVOYA (EVG/c/TAF/FTC) STRIBILD (EVG/c/TDF/FTC)
Raltegravir (RAL)	ISENTRESS:		

ISENTRESS ISENTRESS HD	400-mg tablet 25-mg and 10-mg chewable tablets 100-mg single-use packet for oral suspension ISENTRESS HD: 600-mg tablet		
Other Antiretroviral Classes			
Fusion Inhibitor Enfuvirtide (T-20) FUZEON	FUZEON: Injectable; supplied as lyophilized powder. Each vial contains 108 mg of T-20; reconstitute with 1.1 mL of sterile water for injection for delivery of approximately 90 mg/1 mL.		
CCR5 Antagonist Maraviroc (MVC) SELZENTRY	SELZENTRY: 150-mg and 300-mg tablets		
CD4 Post-Attachment Inhibitor Ibalizumab (IBA) TROGARZO	TROGARZO: Single-dose 2-mL vial containing 200 mg/1.33 mL (150 mg/mL) of ibalizumab		
gp120 Attachment Inhibitor Fostemsavir (FTR) RUKOBIA	600-mg extended-release tablets		
Pharmacokinetic booster (cytochrome p-450 inhibitor) Cobicistat (COBI, c) TYBOST	TYBOST: 150-mg tablets	EVOTAZ: ATV 300-mg/COBI 150-mg tablet PREZCOBIX: DRV 800-mg/COBI 150-mg tablet	SYMTUZA (DRV/c/TAF/FTC) GENVOYA (EVG/c/TAF/FTC) STRIBILD (EVG/c/TDF/FTC)
Abbreviations: Drug abbreviations in Appendix 5; FDC = fixed dose combination; IM = intramuscular; PI = protease inhibitor; STR = single tablet regimen.			

Antiretrovirals can be used to treat and prevent HIV. The goal of treatment is to achieve virologic suppression, which is defined as an HIV RNA (viral load) of less than 50 copies/mL for at least 6 months.[11] The ability to achieve and maintain a suppressed HIV RNA are important endpoints in clinical trials. A virologic blip occurs in patients who achieve suppression and subsequently have an isolated viral load of >200 copies/mL, followed by a return to suppression. Incomplete

virologic response is defined as 2 consecutive viral load measurements of ≥ 200 copies/mL after 24 weeks of ARV treatment when a patient has never had documented virologic suppression on the current regimen. The inability to achieve or maintain suppression with an HIV RNA level of < 200 copies/mL is virologic failure. A virologic blip is not usually associated with later virologic failure. Some data suggest that low level viremia of 50-199 copies/mL can be predictive of later virologic failure and development of drug resistance. Sustained viremia of ≥ 200 copies/mL is associated with virologic failure and the accumulation of viral mutations, and this association is even stronger with persistent viremia of > 500 copies/mL. Virologic failure can be related to many aspects, these include patient adherence related factors (e.g., comorbidities, adverse drug effects, etc), HIV related factors (e.g., presence of transmitted or acquired drug resistance, etc), and ARV regimen factors (e.g., drug-drug interactions, etc).[12] Management of virologic failure should be individualized. Interpretation of resistance test results and management of patients with archived drug-resistance mutations is complicated and generally requires specialist oversight.

Guidance recommends initiation of ART immediately, or as soon as possible after diagnosis.[3-5,11] This has multiple benefits, including improved linkage to care, increased uptake of ART, reduced risk of transmission, and an improved rate of virologic suppression.[3] Initial treatment is dependent on many variables, including comorbidities, virologic efficacy, toxicity, pill burden, resistance test results, drug-drug interactions, and cost. Prevention using ARVs falls into the following main categories: 1) use in infected individuals to maintain HIV RNA below specific thresholds and prevent transmission, and 2) use by uninfected individuals to prevent viral acquisition via pre-exposure prophylaxis (PrEP), occupational and non-occupational post-exposure prophylaxis (PEP), or prophylaxis of newborns with potential perinatal exposure.[3-5]

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 also conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The 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.

Three DERP reports were used to inform recommendations for this drug class: the August 2020 DERP drug class report on Initial Antiretroviral therapies for Treatment-Naïve Individuals with HIV-1: Update (rapid review)[1], the January 2019 DERP report on Prevention and Treatment of HIV-1 Infection: Guidelines[2], and the August 2017 DERP report on Antiretroviral Therapy for HIV-1[13]. The 2017 report findings were updated by the later reports and it will not be described in detail in this document. The original DERP reports are available to Oregon Pharmacy and Therapeutics Committee members upon request. The purpose of the DERP reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. DERP reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. OHSU does not recommend or endorse any guideline or recommendation developed by users of these reports.

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

New Systematic Reviews:
<u>Drug Effectiveness Review Project report on Initial Antiretroviral therapies for Treatment-Naïve Individuals with HIV-1: Update (rapid review)[1]-August 2020</u>

Drug Effectiveness Review Project updated a report on effectiveness and harms of initial first-line HIV-1 therapy. Multiple guidelines were reviewed, including the International Antiviral Society-USA panel (IAS-USA), Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and adolescents (DHHS), European AIDS Clinical Society (EACS), and interim guidelines from the World Health Organization (WHO). Additionally, a total of 21 studies (in 37 publications) were evaluated, and all trials were rated as moderate or high risk of bias.

This report focused on the following key questions in treatment-naïve adults and adolescents infected with HIV-1:

1. What is the comparative effectiveness and harms of recommended antiretroviral backbone medications? Are there differences in effectiveness that would suggest one backbone medication be used over another initially?
2. What is the comparative effectiveness and harms of recommended antiretroviral add-on medications? Are there differences in effectiveness that would suggest one add-on be used over another initially?
3. Are there differences in benefits and harms of antiretroviral therapy regimens across subgroups of HIV-infected patients coinfected with HBV, HCV, or tuberculosis?

Findings related to data on backbone therapies, add-on therapies, and preferred first line therapies are included in **Table 2, Table 3, and Table 4**.

Table 2. Key Findings for Backbone therapies[1]

2-drug vs. 3-drug regimens	**Effectiveness**	**Harms**	**Quality of Evidence**
Lamivudine (3TC) vs. tenofovir disoproxil fumarate/emtricitabine (TDF/FTC)	At 48 weeks, more participants in the 3-drug regimen group (TDF/FTC) achieved viral suppression (HIV-1 RNA < 50 copies/mL) compared to the 2-drug group (3TC); however, the difference was not statistically significant. The 2-drug regimen (3TC) was considered noninferior to the 3-drug regimen.	No participants in either treatment group developed resistance mutations over the course of the study, and there were no numerical differences between groups in serious adverse events (SAEs). At 48 weeks, the 2-drug regimen (3TC) led to smaller increases in serum creatinine compared to the 3-drug regimen (TDF/FTC), indicating less severe kidney effects.	very low to low
3-drug vs. 3-drug regimens	**Effectiveness**	**Harms**	**Quality of Evidence**
Tenofovir alafenamide/emtricitabine (TAF/FTC) vs. TDF/FTC	TAF/FTC was noninferior to TDF/FTC in terms of viral suppression, and the difference between groups was not statistically significant. Few participants developed resistance to study drugs, and there were largely no differences between treatment groups. Adherence was high in both groups, but no significant differences were observed between them.	There were no numerical differences between groups in SAEs; however, TDF/FTC led to significantly greater increases in serum creatinine clearance than TAF/FTC.	very low

TAF/FTC vs. abacavir/lamivudine (ABC/3TC)	TAF/FTC was noninferior to ABC/3TC in terms of viral suppression, and the difference between groups was not statistically significant.	There were no differences between groups in terms of drug resistance, SAEs, or increased serum creatinine level which is indicative of kidney injury.	very low to low
ABC/3TC vs. TDF/FTC	ABC/3TC was noninferior to TDF/FTC and led to a significantly greater percentage of participants achieving viral suppression at 48, 96, and 144 weeks (week 48 adjusted treatment difference DTG+ABC/3TC vs EFV/TDF/FTC 7%; 95% CI 2% to 12%).	There were no resistance mutations in the ABC/3TC group and few resistance mutations in the TDF/FTC group at both 48 and 144 weeks. There was no difference in SAEs between groups. Mean serum creatinine level remained stable through week 144 for patients in the DTG + ABC/3TC group but was not reported for the TDF/FTC group.	very low to moderate
Tenofovir disoproxil fumarate/lamivudine (TDF/3TC) vs. TDF/FTC	TDF/3TC was noninferior to TDF/FTC in terms of viral suppression, and the difference between groups was not statistically significant.	There were fewer resistance mutations in the TDF/3TC group than in the TDF/FTC group. There were no differences in SAEs or increased serum creatinine level indicative of kidney injury between groups.	very low to low

Table 3. Key Findings for Add-on Therapies[1]

3-drug vs. 3-drug regimens	**Effectiveness**	**Harms**	**Quality of Evidence**
Bictegravir (BIC) vs. Dolutegravir (DTG)	BIC was noninferior to DTG in terms of viral suppression, and the treatment difference between groups was not statistically significant.	There were largely no differences between groups in terms of drug resistance, adherence, or increased serum creatinine level indicative of kidney injury. However, there was a greater number of participants with SAEs in the BIC group than in the DTG group, but this was only seen at 96 weeks.	very low to low
Dolutegravir (DTG) vs. Raltegravir (RAL)	DTG was noninferior to RAL in terms of viral suppression, and the difference between treatment groups was not statistically significant.	Few participants in in the RAL group developed resistance to study drugs through week 48. There was no difference between treatment groups in terms of SAEs. There was a greater increase in serum creatinine in the DTG group compared to the RAL group at 48 and 96 weeks.	low to moderate
Darunavir/ritonavir (DRV/r) vs. Doravirine (DOR)	DOR was noninferior to DRV/r in terms of viral suppression, and the difference between groups was not statistically significant.	More DRV/r participants developed resistance to study drugs compared to DOR participants. There was no numerical difference in SAEs between groups and no statistically significant differences in measures of kidney injury or hepatotoxicity between groups at week 96.	low to moderate
DRV/r vs. RAL	Statistically significantly fewer participants achieved viral suppression in the DRV/r group compared to the RAL group (week 96 89.4% vs 93.9%, 95% CI not provided).	Statistically significantly fewer participants experienced drug resistance in the DRV/r group compared to the RAL group (4/601 [0.67%] vs 18/603 [3.0%]). Numerically, more participants in the DRV/r group experienced withdrawals	very low to low

		due to adverse events and hepatic toxicity than participants in the RAL group (no statistical test reported).	
DTG vs. Efavirenz (EFV)	DTG was noninferior to EFV in terms of viral suppression, and the difference between groups was not statistically significant.	There were few participants with virologic failure and resistance mutations overall, and there were largely no differences between treatment groups. There were no differences between groups in terms of adherence to study drugs and SAEs. The effects of DTG and EFV on serum creatinine level were mixed across studies.	low to low
RAL vs. EFV	RAL was noninferior to EFV in terms of viral suppression at 24, 48, 96, and 156 weeks, and there were no statistically significant differences between groups.	There were no differences between treatment groups in terms of drug resistance, adherence to study medications, SAEs, and serum creatinine level indicative of kidney injury.	very low to low
Rilpivirine (RPV) vs. EFV	RPV was noninferior to EFV in terms of viral suppression, and the difference between groups was not statistically significant.	A greater percentage of RPV patients experienced virologic failure and resistance to study drugs than EFV patients. There were no differences between groups in terms of adherence to study medications and SAEs. Participants in the RPV group experienced a small increase in serum creatinine level over the course of the study, but the EFV group experienced no change.	very low to low
Abbreviations: See Appendix 5			

Majority of direct comparative evidence available is in the form of non-inferiority studies. The assessment of subgroups focused on a pooled analysis of the ECHO and THRIVE trials, in which participants received either RPV or EFV in conjunction with a nucleoside reverse transcriptase inhibitor (NRTI)/NRTI backbone. In this analysis, a numerically higher percentage of participants achieved viral suppression in the subgroup without hepatitis B virus (HBV) or hepatitis C virus (HCV) coinfection than in the subgroup with coinfection. Occurrence of hepatic adverse events was low in both treatment groups in the overall population and was higher in patients with HBV or HCV than in those without coinfection.

This report noted limitations relating to lack of generalizability of the study populations. Most participants were white males. Few studies included participants of other genders, races, and ethnicities. This may lead to underrepresentation of severe adverse effects such as HIV-associated nephropathy (HIVAN), which disproportionately affects Black individuals. Few studies reported the percentage of participants with specific HIV risk factors, including MSM, transgender individuals, and PWID. No studies focused on findings in Medicaid populations.

Table 4 below lists guideline recommended first line therapy for most individuals with HIV. Updates for the DHHS guidelines are included later in this document. See **Table 5** for details of methodology and quality for guidelines included in 2019 and 2020 DERP reviews on the treatment and prevention of HIV-1.

Table 4. Guideline Recommended Initial ART Regimens (First-Line Therapy) for Most People with HIV[1]

Regimen	U.S. Trade Name	Guideline Organizations			
		IAS-USA (2018)[14]	DHHS (2019)[15]	EACS (2019)[16]	WHO (2019)[17]
3-drug Regimens: INSTI + 2 NRTIs					
BIC + TAF/FTC	BIKTARVY	x	x	x	
DTG + ABC/3TC	TRIUMEQ	x	x	x	
DTG + TAF/FTC	TIVICAY + DESCOVY	x	x	x	
DTG + TDF/FTC	TIVICAY + TRUVADA		x	x	x
DTG + TDF/3TC	TIVICAY + CIMDUO or TEMIXYS		x	x	x
DTG + TAF/3TC	TIVICAY + VEMLIDY + EPIVIR		x		
RAL + TDF/FTC	ISENTRESS + TRUVADA		x	x	
RAL + TAF/FTC	ISENTRESS + DESCOVY		x	x	
RAL + TDF/3TC	ISENTRESS + CIMDUO or TEMIXYS		x	x	
RAL + TAF/3TC	ISENTRESS + VEMLIDY + EPIVIR		x		
3-drug Regimens: NNRTI + 2 NRTIs					
DOR + TDF/3TC	DELSTRIGO			x	
DOR + TAF/FTC	PIFELTRO + DESCOVY			x	
DOR + TDF/FTC	PIFELTRO + TRUVADA			x	
EFV + TDF/3TC	SYMFI or SYMFI LO				x
EFV + TDF/FTC	ATRIPLA				x
RPV + TAF/FTC	ODEFSEY			x	
RPV + TDF/FTC	COMPLERA			x	
RPV + TDF/3TC	EDURANT + CIMDUO or TEMIXYS			x	
3-drug Regimens: PI/r or PI/c + 2 NRTIs					
DRV/c + TAF/FTC	SYMTUZA			x	
DRV/c + TDF/FTC	PREZCOBIX + TRUVADA			x	
DRV/c + TDF/3TC	PREZCOBIX + CIMDUO or TEMIXYS			x	
DRV/r + TAF/FTC	PREZISTA + NORVIR + DESCOVY			x	
DRV/r + TDF/FTC	PREZISTA + NORVIR + TRUVADA			x	
DRV/r + TDF/3TC	PREZISTA + NORVIR + CIMDUO or TEMIXYS			x	
2-drug Regimen: INSTI + NRTI					
DTG + 3TC	DOVATO		x	x	

Abbreviations: 3TC=lamivudine; ABC=abacavir; BIC=bictegravir; c=cobicistat; DHHS=Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents; DOR=doravirine; DRV=darunavir; DTG=dolutegravir; EACS=European AIDS Clinical Society; EFV=efavirenz; FTC=emtricitabine; IAS-USA=International Antiviral Society-USA Panel; INSTI=integrase strand transfer inhibitor; NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI/c=cobicistat-boosted protease inhibitor; PI/r=ritonavir-boosted protease inhibitor; r=ritonavir; RAL=raltegravir; RPV=rilpivirine; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate; WHO=World Health Organization

Prevention and Treatment of HIV-1 Infection: Guidelines[2]- January 2019

A DERP summary evaluated current guideline recommendations for the treatment and prevention of HIV-1 in adults and adolescents. Eight guidelines were reviewed; 7 included recommendations for pre-exposure prophylaxis (PrEP) and 3 provided recommendations for initial ART regimens for treatment-naïve patients. Guidelines methodologic quality was described as poor, fair, or good **(Table 5)**. See full report for complete descriptions of rating systems used by these guidelines.

Table 5. Clinical Practice Guidelines on Prevention and Treatment of HIV-1[2]

Guideline	Date	Focus	Methodological Quality	Rating System
Australasian Society for HIV, Viral Hepatitis, and Sexual Health Medicine (ASHM)[18]	2018	PrEP	Poor	No grading of evidence or recommendations
British HIV Association/British Association for Sexual Health and HIV (BHIVA/BASHH)[19]	2018	PrEP	Good	GRADE methodology
Canadian Medical Association (CMA)[20]	2018	PrEP	Fair	GRADE methodology
Centers for Disease Control and Prevention (CDC)[21]	2017	PrEP	Good	Strength of recommendations ranges from A to C; quality of evidence for recommendations ranges from I to III
DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents (DHHS)[12]	2018	Treatment	Poor	Strength of recommendations ranges from A to C; quality of evidence for recommendations ranges from I to III
European AIDS Clinical Society (EACS)[16]	2018	PrEP and Treatment	Poor	No grading of evidence or recommendations
International Antiviral Society-USA Panel (IAS-USA)[14]	2018	PrEP and Treatment	Fair	Adapted from Canadian Task Force on Periodic Health Examination
US Preventive Services Task Force (USPSTF) Draft Recommendation*[22]	2018	PrEP	Good	USPSTF rating system

Abbreviations: GRADE=Grading of Recommendations Assessment, Development and Evaluation; PrEP=pre-exposure prophylaxis.
*Finalized June 11, 2019

This report focused on the following key questions:

1. What recommendations do clinical practice guidelines make for preventing and treating HIV-1 infection among adults and adolescents?
2. Do these recommendations differ by patient characteristics (e.g., MSM, PWID)?

Recommendations for PrEP are separated into regimen used and population of use (MSM, heterosexual men and women, PWID, and transgender and gender-diverse people). All guidelines did not include all of these subpopulations, and ratings systems varied **(Table 5)**. Continuous use of daily, oral FTC/TDF 200 mg/300 mg is consistently recommended in all populations by the guidelines. The alternative regimen of on-demand ("2-1-1" or event-driven) dosing of FTC/TDF 200 mg/300 mg was endorsed by most guidelines for MSM and one guideline for transgender and gender-diverse people specifically for use in transgender women. Use of on-demand PrEP was not endorsed by any guideline in heterosexual men and women or PWID, and specifically not recommended by one

guideline in heterosexual men and women given the absence of data. The alternative regimen of TDF alone is not recommended by 2 guidelines in the MSM population due to lack of evidence, and not endorsed by any guideline for transgender and gender-diverse people. The use of TDF alone is recommended as an alternative by several guidelines for heterosexual men and women and PWID **(Table 6)**.

Those beginning PrEP should meeting the following criteria: documented negative HIV test, no signs or symptoms of acute HIV infection, normal renal function, no use of contraindicated medication, and documented vaccination or negative HBV test. Individuals beginning therapy should receive a maximum initial supply of 90-days, with follow-up clinical services and monitoring to support PrEP treatment. These services should include HCV screening, pregnancy testing, access to clean needles/syringes, and substance use treatment services.

Emtricitabine and tenofovir alafenamide (DESCOVY) is absent from this table. It received the FDA indication for use as PrEP in at-risk adults and adolescents weighing at least 35 kg to reduce the risk of HIV-1 infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex on December 3rd, 2019[6], which was after publication of the guidelines included in this summary. Guidelines have not been updated since this approval.

Table 6. Recommendations for PrEP by Patient Population[2]

Regimen	MSM	Heterosexual Men and Women	PWID	Transgender and Gender-Diverse People
Primary Recommended Regimen				
Daily, continuous, oral FTC/TDF 200 mg/300 mg	ASHM • Not rated BHIVA/BASHH • Rating 1A CDC • Rating IA CMA • Strong recommendation; high-quality evidence EACS •Not rated IAS-USA	ASHM • Not rated BHIVA/BASHH • Rating 1A to 2B CDC •Rating IA to IIB CMA • High risk: strong recommendation; high quality of evidence • Low risk: weak recommendation; moderate quality of evidence EACS • Not rated IAS-USA	ASHM • Not rated CDC • Rating IA CMA • Weak recommendation; moderate quality of evidence IAS-USA	ASHM •Not rated BHIVA/BASHH • Rating 1A CMA •Transgender women: strong recommendation; moderate quality of evidence EACS •Not rated IAS-USA

	•Rating AIa USPSTF Rating A	• Rating AIa USPSTF • Rating A	• Rating BIa USPSTF • Rating A	•Rating AIIa USPSTF •Rating A
Alternative Regimens				
On-demand ("2-1-1" or event-driven) dosing of FTC/TDF 200 mg/300 mg	ASHM •Not rated BHIVA/BASHH • Rating 1A CMA • Weak recommendation; high quality of evidence EACS • Not rated IAS-USA • Rating AIa Use NOT recommended if active HBV	BHIVA/BASHH • NR	Not endorsed by any guideline	ASHM •Transgender women: not rated
TDF alone	BHIVA/BASHH •NR CDC •NR	ASHM • Not rated BHIVA/BASHH •Rating A1 CDC •Rating IC USPSTF •Rating A	ASHM • Not rated CDC • Rating IC USPSTF • Rating A	Not endorsed by any guideline

Abbreviations: ASHM=Australasian Society for HIV, Viral Hepatitis and Sexual Medicine; BASHH=British Association for Sexual Health and HIV; BHIV= British HIV Association; CDC=Centers for Disease Control and Prevention; CMA=Canadian Medical Association; EACS=European AIDS Clinical Society; FTC=emtricitabine; HBV=hepatitis B; IAS-USA=International Antiviral Society-USA Panel; MSM=men who have sex with men; NR=not recommended; PWID=people who inject drugs; TDF=tenofovir disoproxil fumarate; USPSTF=US Preventive Services Task Force

Treatment recommendations were included for initial therapy for HIV-1 in treatment-naïve individuals and recommendations for treatment-experienced patients. Initial treatment regimens were divided into those appropriate for most patients and for those with certain clinical conditions (e.g., HLA-B*5701 status, baseline viral load, baseline, etc), but there was limited agreement among the 3 guidelines or details of clinical niche for these regimens. The most up to date initial regimens for most patients were included in the later DERP report and are found in **Table 4.**

Recommendations for switching in treatment-experienced individuals vary among guidelines as well. These include:

- Change from current, older ARV regimens if evidence or potential for chronic toxicity, drug-drug interactions, or emergent adverse effects.[14,16]
- In virologically suppressed patients, consider switching for the following populations:[14]
    - Proactive change from TDF to TAF containing regimens to minimize renal or bone adverse effects (Grade: BIa).
    - Change from 3-drug to specific 2-drug regimens (DTG/RPV [Grade: AIa]; boosted PI with 3TC [Grade: AIIa]; DTG with 3TC [Grade: AIIa]) when there is no prior virologic failure or transmitted drug resistance (long-term follow up needed to assess durability of these strategies).
    - Coinfection with HBV to include regimen with 2 drugs that are active against HBV plus 3rd ARV (Grade: AIIa).
- In situations of virologic failure, multiple factors should be assessed (e.g., adherence, comorbidities, etc.). When switching regimens, the following should be considered:
    - Resistance testing is recommended.
    - DTG plus 2 NRTIs with at least 1 active by genotype is recommended after initial treatment failure with a non-NRTI (Grade: AIa).
    - A boosted PI plus 2 NRTIs (with at least 1 active NRTI) are recommended for initial treatment failure of an INSTI-containing regimen (Grade: AIII).
    - DTG plus at least 1 fully active other agent may be effective in patients with RAL or EVG resistance. DTG should be dosed twice daily (Grade: BIII).
    - Adding a single active agent to a failing regimen is not recommended (Grade: AIa).
    - If multi-class resistance, construct a new regimen using drugs from new classes if available (Grade: BIII).
    - In patients with extensive resistance, maximal virologic suppression might not be possible. Continue ART with regimens designed to minimize toxicity, preserve CD4 count, and delay clinical progression (Grade: AI)
    - When no viable suppressive regimen exists in multidrug-resistant HIV, consider enrollment in a clinical trial or contacting pharmaceutical companies that might have investigational agents available.

After review, 12 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), all trials included had high-risk of bias, outcome studied (e.g., non-clinical), wrong setting of included trials (participants all from low- or middle- income countries), or because study inclusion dates fell within literature search completed by DERP and had already been evaluated (this included 2 high-quality Cochrane reviews).

New Guidelines:
No High-quality guidelines were found since publication of DERP guideline summary.[1,2]

Guidelines for Clinical Context: DHHS guidelines[3-5]
There are multiple iterations of DHHS guidelines related to treatment and prevention of HIV as well as care of HIV infected persons in other situations, including treatment of opportunistic infections. The guidelines received a poor rating of methodological quality due to unclear reporting of methods and potential for numerous biases.[2] They are commonly used in clinical practice and included here for clinical context. The rating system used for recommendations is detailed in **Table 7**.

Table 7. Rating system for DHHS Guideline Recommendations[2-5]

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement	**I:** One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
B: Moderate recommendation for the statement	**II:** One or more well-designed, nonrandomized studies with long-term clinical outcomes
C: Optional recommendation for the statement	**III:** Expert opinion
Abbreviation: DHHS=U.S. Department of Health and Human Services.	

Use of Antiretroviral Agents in Adults and Adolescents with HIV-Update June 3, 2021[3]

General recommendations and details from a past version of this guideline are included in the DERP reports above. The summary below will focus on updates since those publications.

Recommendations for use of DTG/3TC as an initial regimen in most people with HIV (Grade AI), except for individuals

- With pre-treatment HIV RNA >500,000 copies/mL;
- With active hepatitis B virus (HBV) coinfection; or
- Who will begin ART before results of HIV genotype testing for reverse transcriptase or HBV testing are available.

Information regarding the use of certain agents, including DTG based regimens, and cabotegravir with rilpivirine in individuals of childbearing potential have been updated. New data show that the risk of neural tube defects (NTDs) with DTG use near time of conception may be is much lower than 0.9% incidence originally reported, and is now estimated at 0.19% compared to 0.09% in women receiving non-DTG containing regimens and 0.12% in women without HIV. These differences were not found to be statistically significant; furthermore, lack of folate consumption due to the uncommon fortification of grains at the location of the initial data may have been an additional confounder. The updated recommendations include:

- Discussion of the benefits of using DTG and the risk of NTDs with the person of childbearing potential, to allow for informed decision making.
- A dual NRTI with DTG or RAL remain preferred options for individuals who are trying to conceive (Grade AIII).
- Cabotegravir with rilpivirine long-acting injectable is not recommended, as it has not been studied, in those trying to conceive (Grade AIII).

Recommendations for ART use in women were updated to note that initiating and changing ART may result in weight gain. Women, and specifically Black women, generally experience more weight gain than men (Grade AI). This may be higher with DTG or BIC based regimens. The quantity of weight gained varied by study; including ≥ 10% weight gain (17.4% female vs 12.2% male; 19.7% Black females vs. 12.4% non-Black females) and 4.2 kg gain in women switching to or adding an INSTI to 0.2 kg for women remaining on non-INSTI regimens after 2 years.

Additional updates include an emphasis on the importance of screening and early diagnosis of HIV, with a recommendation to begin ART immediately or as soon as possible after diagnosis (Grade AII). The regimen of BIC/TAF/FTC was added as an option to treat individuals with acute or recent infection before genotypic drug resistance testing results are available. RAL based regimens have been moved from “Recommended Initial Regimens for Most People with HIV” to one recommended for “certain clinical situations” (Grade BI) due to several reasons. It is no longer necessary to choose RAL over DTG for individuals who may become pregnant, RAL has a lower barrier to resistance than DTB or BIC, and RAL based regimens have a higher pill burden than other INSTI options.

Recommendations related to virologic failure edited the wording that a new regimen "should contain at least 2, and preferably 3, fully active agents (Grade AI)" to "can include 2 fully active agents if at least one with a high resistance barrier is included (e.g., DTG or boosted DRV) (Grade AI)".

Use of Antiretroviral Agents in Pediatric HIV Infection-Update April 7, 2021[4]

The early use of ART has shown benefit in all children living with HIV. These benefits include control of viral replication, fewer drug-resistance mutations, preservation of immune function, prevention of clinical disease progression, possible reduction of inflammation mediated non-AIDS complications (e.g., cardiovascular, kidney, and liver disease, and malignancy), and improved survival. ART should be initiated immediately, or as soon as possible after diagnosis.

Initial preferred therapy in children is dependent on age and weight. Much of the data related to the use of INSTI regimens consists of non-comparative studies of safety, tolerability, and pharmacokinetics of these agents. Clinical effectiveness is commonly extrapolated from adult comparative trials and smaller studies in treatment-naïve adolescents.

Preferred regimens in children (in combination with 2 NRTI backbone):

- Newborns age <14 days: NVP
- Newborns age <4 weeks and weighing ≥ 2kg: RAL
- Neonates age ≥ 14 days to < 4 weeks: LPV/r
- Infants and Children age ≥ 4 weeks and weighing ≥ 3 kg: DTG
- Children age ≥ 6 years and weighing ≥ 25 kg: DTG or BIC
- Adolescents age ≥ 12 years with sexual maturity rating of 4 or 5 should refer to Adult and Adolescent guidelines

The recommended dual NRTI backbone varies by age and most frequently includes ZDV plus (3TC or FTC) for children under 1 month, ABC plus (3TC or FTC) between 1 month and 6 years, and ABC plus (3TC or FTC) or FTC/TAF (in specific circumstances) from 6 to 12 years. Full recommendations and alternative regimens are found in the guidelines.

Use of Antiretroviral Agents in in Pregnant Women with HIV infection and Interventions to Reduce Perinatal HIV transmission in the United States-Update Feb 10, 2021 [5]

All pregnant individuals who are HIV positive and pregnant should initiate ART as soon as possible to maximize health and minimize transmission (Grade AI), and earlier viral suppression has been associated with a lower risk of transmission. Individuals should be counseled on different treatment options to allow for informed decision making. All treatment choices should be individualized, and initial treatment recommendations for pregnant individuals can be found in **Table 8**.

Table 8. Initial ART in Treatment-Naïve Pregnant Individuals[5]

Preferred Regimens in Pregnancy
Preferred Dual-NRTI Backbones
ABC/3TC
TDF/FTC ***or*** TDF/3TC
Preferred INSTI Regimens
DTG/ABC/3TC (FDC) ***or*** DTG plus a Preferred Dual-NRTI Backbone
RAL plus a Preferred Dual-NRTI Backbone
Preferred PI Regimens
ATV/r plus a Preferred Dual-NRTI Backbone
DRV/r plus a Preferred Dual-NRTI Backbone
Alternative Regimens in Pregnancy
Alternative Dual-NRTI Backbones
TAF/FTC
ZDV/3TC
Alternative NNRTI Regimens
EFV/TDF/FTC (FDC) ***or*** EFV/TDF/3TC (FDC) ***or*** EFV plus a Preferred Dual-NRTI Backbone
RPV/TDF/FTC (FDC) ***or*** RPV/TAF/FTC (FDC) RPV plus a Preferred Dual-NRTI Backbone
Insufficient Data in Pregnancy to Recommend for Initial Regimens in ART-Naïve Individuals
BIC/TAF/FTC (FDC)
DOR
IBA
Not Recommended for Initial ART or Use in Pregnancy
ATV/c
DRV/c (FDC) ***or*** DRV/c/FTC/TAF (FDC)
EVG/c/FTC/TAF (FDC)
EVG/c/FTC/TDF (FDC)
Not Recommended for Initial ART in Pregnancy and Not Recommended, Except in Special Circumstances, for Treatment-Experienced Individuals in Pregnancy
ETR
LPV/r plus a Preferred Dual-NRTI Backbone
MVC
NVP
T-20
Any of the follow drugs or combinations: d4T, ddI, FPV, FPV/r, IDV, IDV/r, NFV, RTV (as the sole PI), SQV, SQV/r, TPV, TPV/r, two-drug ARV regimens, or a three-NRTI ARV regimen

Abbreviations: 3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; CD4 = CD4 T lymphocyte cell; COBI = cobicistat; d4T = stavudine; ddI = didanosine; DOR = doravirine; DRV = darunavir; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDC = fixed-dose combination; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; FTC = emtricitabine; IBA = ibalizumab; IDV = indinavir; IDV/r = indinavir/ritonavir; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NTD = neural tube defect; NVP = nevirapine; the Panel = the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission; PI = protease inhibitor; PK = pharmacokinetic; PPI = proton pump inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQV = saquinavir; SQV/r = saquinavir/ritonavir; T-20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; TPV/r = tipranavir/ritonavir; ZDV = zidovudine

In newborns of individuals of with HIV, ART use is divided into:

- ART prophylaxis: administration of single agent (typically ZDV), or 2 to 3 drug regimens to reduce risk of HIV acquisition
- Presumptive HIV therapy: administration of 3-drug regimen to newborns at high risk of HIV acquisition; this therapy serves as treatment or prophylaxis
- HIV therapy: administration of 3-drug regimen in newborn with documented infection

These therapies should be initiated as soon as possible after delivery. Recommended regimens can be found in **Table 9.**

Table 9. Drug recommendations for ART in Newborns[5]

Newborns at Low Risk of Perinatal HIV Transmission	
Recommended Regimen	Recommended Duration
ZDV	4 weeks
Newborns at High Risk of Perinatal HIV Transmission	
Recommended Regimen	Recommended Duration
Three-drug HIV therapy: ZDV plus 3TC plus (NVP *or* RAL)	Optimal duration unknown and dependent on many factors. ZDV should be given for 6 weeks 3TC, NVP, and RAL duration may vary from 2 to 6 weeks
Newborns with HIV Infection	
Recommended Regimen	Recommended Duration
Three-drug HIV therapy: ZDV plus 3TC plus (NVP *or* RAL)	Lifelong therapy, agents may change with age per current treatment guidelines
Abbreviations: 3TC=lamivudine; NVP=nevirapine; RAL=raltegravir; ZDV = zidovudine	

No guidelines were excluded due to poor quality, see 2019 DERP report above for full discussion of available guidelines.

New Formulations or Indications:
See **Table 1** for current list of available formulations for prevention and treatment of HIV.

New FDA Safety Alerts:
None

Randomized Controlled Trials:

A total of 218 citations were manually reviewed from the initial literature search. After further review, 217 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), outcome studied (e.g., non-clinical, extension study of secondary endpoints), or were covered in the accompanying new drug evaluation on cabotegravir. The remaining trial is summarized in the table below. The full abstracts is included in **Appendix 2**.

Table 10. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Mayer et al.[7] MC, DB, DD, RCT, NI 96 weeks, then offered OL enrollment	1. emtricitabine 200mg/ tenofovir alafenamide 25 mg N=2670 FAS 2. emtricitabine 200mg/ tenofovir disoproxil fumarate 300 mg N=2665 FAS FAS=randomized, received at least 1 dose study drug, had a least 1 post-baseline HIV test.	HIV negative cisgender MSM and transgender women at high risk of HIV acquisition	Incident HIV infection in full analysis set once all patients had been treated a minimum of 48 weeks and at least 50% had duration of treatment for 96 weeks.	Group 1 vs. Group 2 IRR 0.47 (95% CI 0.19-1.15); met pre-specified non-inferiority criteria HIV infections 1. 7 infections, 4370 person-years (1 suspected acquisition prior to baseline; tested negative at baseline & positive at week 4) 2. 15 infections, 4386 person-years (4 suspected acquisitions prior to baseline; tested negative at baseline & positive at week 4)
Abbreviations: ART=antiretroviral treatment; CI=confidence interval; DB=double-blind; DD=double dummy; FAS=full analysis set; IRR=incident rate ratio; MC=multicenter; mg = milligram; MSM=men who have sex with men; NI=non-inferiority; OL = open label; RCT = randomized clinical trial				

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
abacavir sulfate	ABACAVIR	ORAL	SOLUTION	Y
abacavir sulfate	ZIAGEN	ORAL	SOLUTION	Y
abacavir sulfate	ABACAVIR	ORAL	TABLET	Y
abacavir sulfate	ZIAGEN	ORAL	TABLET	Y
abacavir sulfate/lamivudine	ABACAVIR-LAMIVUDINE	ORAL	TABLET	Y
abacavir sulfate/lamivudine	EPZICOM	ORAL	TABLET	Y
abacavir/dolutegravir/lamivudi	TRIUMEQ	ORAL	TABLET	Y
abacavir/lamivudine/zidovudine	ABACAVIR-LAMIVUDINE-ZIDOVUDINE	ORAL	TABLET	Y
abacavir/lamivudine/zidovudine	TRIZIVIR	ORAL	TABLET	Y
atazanavir sulfate	ATAZANAVIR SULFATE	ORAL	CAPSULE	Y
atazanavir sulfate	REYATAZ	ORAL	CAPSULE	Y
atazanavir sulfate	REYATAZ	ORAL	POWD PACK	Y
atazanavir sulfate/cobicistat	EVOTAZ	ORAL	TABLET	Y
bictegrav/emtricit/tenofov ala	BIKTARVY	ORAL	TABLET	Y
cabotegravir sodium	VOCABRIA	ORAL	TABLET	Y
cabotegravir/rilpivirine	CABENUVA	INTRAMUSC	SUSER VIAL	Y
cobicistat	TYBOST	ORAL	TABLET	Y
darunavir ethanolate	PREZISTA	ORAL	ORAL SUSP	Y
darunavir ethanolate	PREZISTA	ORAL	TABLET	Y
darunavir/cob/emtri/tenof alaf	SYMTUZA	ORAL	TABLET	Y
darunavir/cobicistat	PREZCOBIX	ORAL	TABLET	Y
didanosine	DIDANOSINE	ORAL	CAPSULE DR	Y
didanosine	VIDEX EC	ORAL	CAPSULE DR	Y
didanosine/sodium citrate	VIDEX	ORAL	PACKET	Y
dolutegravir sodium	TIVICAY PD	ORAL	TAB SUSP	Y
dolutegravir sodium	TIVICAY	ORAL	TABLET	Y
dolutegravir sodium/lamivudine	DOVATO	ORAL	TABLET	Y
dolutegravir/rilpivirine	JULUCA	ORAL	TABLET	Y
doravirine	PIFELTRO	ORAL	TABLET	Y
doravirine/lamivu/tenofov diso	DELSTRIGO	ORAL	TABLET	Y
efavirenz	EFAVIRENZ	ORAL	CAPSULE	Y
efavirenz	SUSTIVA	ORAL	CAPSULE	Y
efavirenz	EFAVIRENZ	ORAL	TABLET	Y
efavirenz	SUSTIVA	ORAL	TABLET	Y
efavirenz/emtricit/tenofovr df	ATRIPLA	ORAL	TABLET	Y
efavirenz/emtricit/tenofovr df	EFAVIRENZ-EMTRIC-TENOFOV DISOP	ORAL	TABLET	Y
efavirenz/lamivu/tenofov disop	EFAVIRENZ-LAMIVU-TENOFOV DISOP	ORAL	TABLET	Y

efavirenz/lamivu/tenofov disop	SYMFI	ORAL	TABLET	Y
efavirenz/lamivu/tenofov disop	SYMFI LO	ORAL	TABLET	Y
elviteg/cob/emtri/tenof alafen	GENVOYA	ORAL	TABLET	Y
elviteg/cob/emtri/tenofo disop	STRIBILD	ORAL	TABLET	Y
emtricita/rilpivirine/tenof DF	COMPLERA	ORAL	TABLET	Y
emtricitab/rilpiviri/tenof ala	ODEFSEY	ORAL	TABLET	Y
emtricitabine	EMTRICITABINE	ORAL	CAPSULE	Y
emtricitabine	EMTRIVA	ORAL	CAPSULE	Y
emtricitabine	EMTRIVA	ORAL	SOLUTION	Y
emtricitabine/tenofov alafenam	DESCOVY	ORAL	TABLET	Y
emtricitabine/tenofovir (TDF)	EMTRICITABINE-TENOFOVIR DISOP	ORAL	TABLET	Y
emtricitabine/tenofovir (TDF)	TRUVADA	ORAL	TABLET	Y
enfuvirtide	FUZEON	SUB-Q	VIAL	Y
etravirine	INTELENCE	ORAL	TABLET	Y
fosamprenavir calcium	LEXIVA	ORAL	ORAL SUSP	Y
fosamprenavir calcium	FOSAMPRENAVIR CALCIUM	ORAL	TABLET	Y
fosamprenavir calcium	LEXIVA	ORAL	TABLET	Y
ibalizumab-uiyk	TROGARZO	INTRAVEN	VIAL	Y
indinavir sulfate	CRIXIVAN	ORAL	CAPSULE	Y
lamivudine	EPIVIR	ORAL	SOLUTION	Y
lamivudine	LAMIVUDINE	ORAL	SOLUTION	Y
lamivudine	EPIVIR	ORAL	TABLET	Y
lamivudine	LAMIVUDINE	ORAL	TABLET	Y
lamivudine/tenofovir disop fum	CIMDUO	ORAL	TABLET	Y
lamivudine/tenofovir disop fum	TEMIXYS	ORAL	TABLET	Y
lamivudine/zidovudine	COMBIVIR	ORAL	TABLET	Y
lamivudine/zidovudine	LAMIVUDINE-ZIDOVUDINE	ORAL	TABLET	Y
lopinavir/ritonavir	KALETRA	ORAL	SOLUTION	Y
lopinavir/ritonavir	LOPINAVIR-RITONAVIR	ORAL	SOLUTION	Y
lopinavir/ritonavir	KALETRA	ORAL	TABLET	Y
maraviroc	SELZENTRY	ORAL	SOLUTION	Y
maraviroc	SELZENTRY	ORAL	TABLET	Y
nelfinavir mesylate	VIRACEPT	ORAL	TABLET	Y
nevirapine	NEVIRAPINE	ORAL	ORAL SUSP	Y
nevirapine	VIRAMUNE	ORAL	ORAL SUSP	Y
nevirapine	NEVIRAPINE ER	ORAL	TAB ER 24H	Y
nevirapine	VIRAMUNE XR	ORAL	TAB ER 24H	Y
nevirapine	NEVIRAPINE	ORAL	TABLET	Y
nevirapine	VIRAMUNE	ORAL	TABLET	Y
raltegravir potassium	ISENTRESS	ORAL	POWD PACK	Y

raltegravir potassium	ISENTRESS	ORAL	TAB CHEW	Y
raltegravir potassium	ISENTRESS	ORAL	TABLET	Y
raltegravir potassium	ISENTRESS HD	ORAL	TABLET	Y
rilpivirine HCl	EDURANT	ORAL	TABLET	Y
ritonavir	NORVIR	ORAL	POWD PACK	Y
ritonavir	NORVIR	ORAL	SOLUTION	Y
ritonavir	NORVIR	ORAL	TABLET	Y
ritonavir	RITONAVIR	ORAL	TABLET	Y
saquinavir mesylate	INVIRASE	ORAL	TABLET	Y
stavudine	STAVUDINE	ORAL	CAPSULE	Y
tipranavir	APTIVUS	ORAL	CAPSULE	Y
tipranavir/vitamin E TPGS	APTIVUS	ORAL	SOLUTION	Y
zidovudine	RETROVIR	ORAL	CAPSULE	Y
zidovudine	ZIDOVUDINE	ORAL	CAPSULE	Y
zidovudine	RETROVIR	ORAL	SYRUP	Y
zidovudine	ZIDOVUDINE	ORAL	SYRUP	Y
zidovudine	ZIDOVUDINE	ORAL	TABLET	Y
zidovudine	RETROVIR	INTRAVEN	VIAL	Y

Appendix 2: Abstracts of Comparative Clinical Trials

Emtricitabine and tenofovir alafenamide vs emtricitabine and tenofovir disoproxil fumarate for HIV pre-exposure prophylaxis (DISCOVER): primary results from a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial[7]

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Summary

Background Tenofovir alafenamide shows high antiviral efficacy and improved renal and bone safety compared with tenofovir disoproxil fumarate when used for HIV treatment. Here, we report primary results from a blinded phase 3 study evaluating the efficacy and safety of pre-exposure prophylaxis (PrEP) with emtricitabine and tenofovir alafenamide versus emtricitabine and tenofovir disoproxil fumarate for HIV prevention.

Methods This study is an ongoing, randomised, double-blind, multicentre, active-controlled, phase 3, noninferiority trial done at 94 community, public health, and hospital-associated clinics located in regions of Europe and North America, where there is a high incidence of HIV or prevalence of people living with HIV, or both. We enrolled adult cisgender men who have sex with men and transgender women who have sex with men, both with a high risk of acquiring HIV on the basis of their self-reported sexual behaviour in the past 12 weeks or their recent history (within 24 weeks of enrolment) of bacterial sexually transmitted infections. Participants with current or previous use of PrEP with emtricitabine and tenofovir disoproxil fumarate were not excluded. We used a computer-generated random allocation sequence to randomly assign (1:1) participants to receive either emtricitabine (200 mg) and tenofovir alafenamide (25 mg) tablets daily, with matched placebo tablets (emtricitabine and tenofovir alafenamide group), or emtricitabine (200 mg) and tenofovir disoproxil fumarate (300 mg) tablets daily, with matched placebo tablets (emtricitabine and tenofovir disoproxil fumarate group). As such, all participants were given two tablets. The trial sponsor, investigators, participants, and the study staff who provided the study drugs, assessed the outcomes, and collected the data were masked to group assignment. The primary efficacy outcome was incident HIV infection, which was assessed when all participants had completed 48 weeks of followup and half of all participants had completed 96 weeks of follow-up. This full analysis set included all randomly assigned participants who had received at least one dose of the assigned study drug and had at least one postbaseline HIV test. Non-inferiority of emtricitabine and tenofovir alafenamide to emtricitabine and tenofovir disoproxil fumarate was established if the upper bound of the 95·003% CI of the HIV incidence rate ratio (IRR) was less than the prespecified non-inferiority margin of 1·62. We prespecified six secondary bone mineral density and renal biomarker safety endpoints to evaluate using the safety analysis set. This analysis set included all randomly assigned participants who had received at least one dose of the assigned study drug. This trial is registered with ClinicalTrials.gov, NCT02842086, and is no longer recruiting.

Findings Between Sept 13, 2016, and June 30, 2017, 5387 (92%) of 5857 participants were randomly assigned and received emtricitabine and tenofovir alafenamide (n=2694) or emtricitabine and tenofovir disoproxil fumarate (n=2693). At the time of the primary efficacy analysis (ie, when all participants had completed 48 weeks and 50% had completed 96 weeks) emtricitabine and tenofovir alafenamide was non-inferior to emtricitabine and tenofovir disoproxil fumarate for HIV prevention, as the upper limit of the 95% CI of the IRR, was less than the prespecified non-inferiority margin of 1·62 (IRR 0·47 [95% CI 0·19–1·15]). After 8756 person-years of follow-up, 22 participants were diagnosed with HIV, seven participants in the emtricitabine and tenofovir alafenamide group (0·16 infections per 100 person-years [95% CI 0·06–0·33]), and 15 participants in the emtricitabine and tenofovir disoproxil fumarate group (0·34 infections per 100 person-years [0·19–0·56]). Both regimens were well tolerated, with a low number of participants reporting adverse events that led to discontinuation of the study drug (36 [1%] of 2694 participants in the emtricitabine and tenofovir alafenamide group vs 49 [2%] of 2693 participants in the emtricitabine and tenofovir

disoproxil fumarate group). Emtricitabine and tenofovir alafenamide was superior to emtricitabine and tenofovir disoproxil fumarate in all six prespecified bone mineral density and renal biomarker safety endpoints.

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 May 24, 2021

		Searches	Results
○	1	abacavir.mp.	2443
○	2	atazanavir.mp. or Atazanavir Sulfate/	1908
○	3	bictegravir.mp.	148
○	4	cabotegravir.mp.	174
○	5	Cobicistat/ or cobicistat.mp.	600
○	6	darunavir.mp. or Darunavir/	1812
○	7	didanosine.mp. or Didanosine/	2830
○	8	dolutegravir.mp.	1346
○	9	doravirine.mp.	116
○	10	efavirenz.mp. or Efavirenz, Emtricitabine, Tenofovir Disoproxil Fumarate Drug Combination/	4854
○	11	elvitegravir.mp. or Elvitegravir, Cobicistat, Emtricitabine, Tenofovir Disoproxil Fumarate Drug Combination/	738
○	12	Efavirenz, Emtricitabine, Tenofovir Disoproxil Fumarate Drug Combination/ or Emtricitabine, Rilpivirine, Tenofovir Drug Combination/ or Emtricitabine/ or Elvitegravir, Cobicistat, Emtricitabine, Tenofovir Disoproxil Fumarate Drug Combination/ or Emtricitabine, Tenofovir Disoproxil Fumarate Drug Combination/ or emtricitabine.mp.	3117
○	13	enfuvirtide.mp. or Enfuvirtide/	1033
○	14	etravirine.mp.	791
○	15	fosamprenavir.mp.	286
○	16	ibalizumab.mp.	71
○	17	indinavir.mp. or Indinavir/	2772
○	18	lamivudine.mp. or Lamivudine/	10341
○	19	lopinavir.mp. or Lopinavir/	3850
○	20	maraviroc.mp. or Maraviroc/	1184
○	21	nelfinavir.mp. or Nelfinavir/	1912
○	22	nevirapine.mp. or Nevirapine/	4706
○	23	raltegravir.mp. or Raltegravir Potassium/	2031
○	24	Emtricitabine, Rilpivirine, Tenofovir Drug Combination/ or Rilpivirine/ or rilpivirine.mp.	792
○	25	ritonavir.mp. or Ritonavir/	8062
○	26	saquinavir.mp. or Saquinavir/	2135
○	27	stavudine.mp. or Stavudine/	3012
○	28	tipranavir.mp.	483
○	29	zidovudine.mp. or Zidovudine/	12584
○	30	Efavirenz, Emtricitabine, Tenofovir Disoproxil Fumarate Drug Combination/ or Emtricitabine, Rilpivirine, Tenofovir Drug Combination/ or Tenofovir/ or Elvitegravir, Cobicistat, Emtricitabine, Tenofovir Disoproxil Fumarate Drug Combination/ or Emtricitabine, Tenofovir Disoproxil Fumarate Drug Combination/ or tenofovir.mp.	8072
○	31	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 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30	46949
○	32	limit 31 to yr="2015 -Current"	12598
○	33	limit 32 to english language	12322
○	34	limit 33 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or randomized controlled trial or "systematic review")	2149
○	35	COVID-19/	79953
○	36	SARS Virus/ or SARS-CoV-2/ or SARS.mp.	95070
○	37	Middle East Respiratory Syndrome Coronavirus/	1620
○	38	35 or 36 or 37	110646
○	39	34 not 38	2011
◉	40	limit 39 to yr="2020 -Current"	227

Appendix 4: Key Inclusion Criteria

Population	Adults and children with HIV-1 or at risk of acquiring HIV-1
Intervention	See Appendix 1
Comparator	See Appendix 1, placebo
Outcomes	HIV RNA copies, HIV acquisition
Timing	Prophylaxis or Treatment
Setting	Outpatient

Appendix 5: Abbreviations for Antiretroviral Drug Names[12]

3TC	lamivudine
ABC	abacavir
APV	amprenavir
ATV	atazanavir
BIC	bictegravir
CAB	cabotegravir
COBI or c	cobicistat
d4T	stavudine
ddI	didanosine
DLV	delavirdine
DOR	doravirine
DRV	darunavir
DTG	dolutegravir
EFV	efavirenz
ETR	etravirine
EVG	elvitegravir
FPV	fosamprenavir
FTC	emtricitabine
IBA	ibalizumab
IDV	indinavir
LPV	lopinavir
MVC	maraviroc

NFV	nelfinavir
NVP	nevirapine
RAL	raltegravir
RPV	rilpivirine
RTV or r	ritonavir
SQV	saquinavir
T-20	enfuvirtide
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TPV	tipranavir
ZDV	zidovudine

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
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New Drug Evaluation: Cabotegravir/Rilpivirine Inj; Cabotegravir Na Tab

Date of Review: August 2021
Generic Name: Cabotegravir/rilpivirine inj; Cabotegravir sodium tab

End Date of Literature Search: 05/31/2021
Brand Name (Manufacturer): Cabenuva, Vocabria (GlaxoSmithKline)
Dossier Received: yes

Research Questions:

1. How does the Human Immunodeficiency Virus (HIV-1) viral suppression differ between the monthly 2-drug antiretroviral drug regimen of extended-release injectable cabotegravir and rilpivirine from standard, guideline-recommended 3-drug antiretroviral regimens?
2. Do adverse effects and other harms differ between the monthly 2-drug antiretroviral drug regimen of extended-release injectable cabotegravir and rilpivirine from standard, guideline-recommended 3-drug antiretroviral regimens?
3. Are there subgroups based on demographic characteristics in which the monthly 2-drug antiretroviral drug regimen of extended-release injectable cabotegravir and rilpivirine may differ in safety or efficacy from standard, guideline-recommended 3-drug antiretroviral regimens?

Conclusions:

- Low quality evidence demonstrates that monthly injections of cabotegravir and rilpivirine are non-inferior to standard, 3-drug antiretroviral drug regimens in adults with HIV who are virologically stable and suppressed (HIV-1 RNA <50 copies/mL). The phase 3 trials were well designed, but the evidence was downgraded because of the open-label design and the caveat that uncertainty remains about the durability of these benefits beyond 48 weeks of treatment.[1-3]
- Low quality evidence also demonstrates that extended-release injectable cabotegravir and rilpivirine is associated with similar harms as other antiretroviral regimens. The proportion of patients in the extended-release injectable group who experienced adverse effects was greater than in the oral group which was partly attributable to various injection site reactions. Injection site pain was the most commonly reported injection site reaction, which occurred in up to 90% of patients; incidence decreased over the 48-week study periods.[1-3]
- Rates of virologic failure were higher for the extended-release injectable cabotegravir and rilpivirine regimen versus 3-drug oral therapy in females, patients with a higher baseline body mass index (BMI ≥30 kg/m^2) and females with a higher baseline BMI (BMI ≥30 kg/m^2); evidence for these subgroup analyses is insufficient and further evaluation is warranted.[1] The evidence for safety and efficacy of extended-release injectable cabotegravir and rilpivirine is also insufficient among patients who have a baseline K103N substitution, acquired integrase strand transfer inhibitor or non-nucleoside reverse transcriptase inhibitor resistance, or with history of treatment failure.[1]

Author: Andrew Gibler, PharmD

Recommendations:

- It is unclear whether there is an unmet clinical need for monthly antiretroviral (ARV) injectable regimens given that all oral ARV treatments options are currently on the Oregon Health Plan (OHP) Preferred Drug List (PDL). However, some patients may prefer the convenience of monthly injections versus daily oral treatment and there is potential, albeit without evidence to date, that this injectable regimen may improve adherence in specific patients. Therefore, it is recommended to add cabotegravir tablets and extended-release injectable suspension to the OHP PDL.

Background:

Chronic HIV infection has been effectively managed with diligent, life-long adherence to combination oral ARV treatment. The current ARV treatment options approved by the FDA include 29 individual ARV drugs, excluding combination products, and 2 drugs (cobicistat and ritonavir) which inhibit metabolic enzymes and increase the exposure of ARVs.[1] However, optimal management of HIV is complex and is based on individual patient needs. One opportunity to simplify ARV regimens is to extend the dosing interval with the use of long-acting ARV agents. On January 21, 2021, the U.S. Food and Drug Administration (FDA) approved the first complete extended-release (ER) injectable ARV regimen, cabotegravir and rilpivirine, in adults with HIV who are virologically stable and suppressed (HIV-1 RNA <50 copies/mL).[4] The co-packaged kit contains separate ER injectable suspensions of cabotegravir and rilpivirine (CABENUVA).[4] Cabotegravir was also developed as an oral tablet (VOCABRIA) to use in combination with oral rilpivirine.[5] In theory, monthly injections of a 2-drug ARV regimen could reduce the complexity of daily oral ARV treatment and decrease the risk of adverse effects of the third drug in a standard 3-drug ARV regimen.[1]

Cabotegravir is a second-generation integrase strand transfer inhibitor (INSTI) structurally similar to dolutegravir. Rilpivirine is a second-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) already approved by the FDA. Both INSTIs and NNRTIs are included in most standard, guideline-recommended 3-drug ARV regimens.[6]

The cabotegravir and rilpivirine regimen consists of 2 separate once-monthly injections of cabotegravir and rilpivirine administered by a healthcare professional preceded by an oral lead-in trial of at least 28 days during which oral cabotegravir and rilpivirine tablets are taken in combination to ensure patient tolerability and verify virologic suppression (HIV-1 RNA <50 copies/mL).[4,5] Cabotegravir tablets are indicated either as an oral lead-in to assess tolerability of cabotegravir before initiating cabotegravir and rilpivirine injections, or as oral bridging therapy for missed cabotegravir and rilpivirine injections.[5]

The recommended dosage for the cabotegravir plus rilpivirine regimen consists of 3 distinct phases:

1. Oral lead-in phase: One cabotegravir 30 mg tablet and one rilpivirine 25 mg tablet taken together once daily for approximately one month;
2. Single initiation injections of cabotegravir plus rilpivirine (600 mg/900 mg, 3 mL each in separate gluteal sites) on the last day of the oral lead-in phase; and
3. Monthly maintenance injections of cabotegravir plus rilpivirine (400 mg/600 mg, 2 mL each in separate gluteal sites).

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

Clinical Efficacy:

Cabotegravir and rilpivirine was studied in two randomized, open-label, multi-centered, active-controlled, noninferiority phase 3 trials: ATLAS (Antiretroviral Therapy as Long Acting Suppression; NCT02951052) in adult patients who were already stable on oral ARV therapy, and FLAIR (First Long-Acting Injectable

Regimen; NCT02938520) in ARV-naïve adult patients.[2,3] Together, the trials enrolled 1,182 patients. Patients in both trials were virologically suppressed before randomization and then either switched to cabotegravir plus rilpivirine or continued current oral 3-drug ARV therapy.[2,3] In both trials, the ER cabotegravir and rilpivirine injectable regimen demonstrated noninferiority to the comparative oral ARV regimens based on the proportion of patients with a serum HIV-1 RNA level of 50 copies per milliliter or higher at week 48 using a noninferiority margin of 6%.[2,3]

The ATLAS trial was a 48-week, randomized, multi-center, open-label, non-inferiority, parallel-group trial that enrolled HIV-infected adult patients 18 years of age or older who were virologically suppressed on oral ARV therapy.[2] The purpose of the ATLAS trial was to establish whether switching to ER injectable cabotegravir and rilpivirine was noninferior to continuation of current oral therapy based on virologic response.[2] Key pertinent details and analysis of the trial are presented in **Table 1**. Eligible patients were randomly assigned in a 1-to-1 ratio to either continue their current oral ARV regimen or switch to cabotegravir and rilpivirine.[2] Acceptable current ARV regimens included two NRTIs plus one of the following drugs: an INSTI, an NNRTI, a boosted PI, or unboosted atazanavir.[2] Patients in the ER injectable therapy group first received 30 mg oral cabotegravir and 25 mg oral rilpivirine once daily with food for the first 4 weeks (oral lead-in phase) to assess safety and adverse effects.[2] After their eligibility for ER injectable therapy was confirmed, patients received an initial dose of 600 mg cabotegravir and 900 mg rilpivirine (3 mL injections of each drug into the gluteus muscle), followed by 400 mg cabotegravir and 600 mg rilpivirine (2 mL injections of each drug into the gluteus muscle) every 4 weeks through week 52 of the maintenance phase of the trial.[2] Oral cabotegravir and rilpivirine was available as bridge therapy for patients who were unable to attend their scheduled clinic visit within the permitted window (21 to 28 days after the previous injection for injections 2 and 3; 21 to 35 days thereafter).[2]

The primary endpoint was the percentage of patients with plasma HIV-1 RNA levels of 50 copies per milliliter or higher at week 48.[2] The key secondary efficacy endpoint was the percentage of patients with plasma HIV-1 RNA levels of less than 50 copies per milliliter at week 48.[2] Other endpoints included confirmed virologic failure (two consecutive plasma HIV-1 RNA measurements ≥200 copies/mL) and patient satisfaction with their current ARV therapy assessed at baseline and at weeks 24 and 44 with the 12-item HIV Treatment Satisfaction Questionnaire, status version (HIVTSQs).[2] The HIVTSQs assesses change in within-participant treatment satisfaction over time and is a variation of the HIV Medication Questionnaire, which was adapted from the Renal Medication Questionnaire.[7] Of note, no minimal clinically important difference has been established for the HIVTSQs in patients with HIV-1 infection.[8]

In the ATLAS trial, HIV-1 RNA levels of 50 copies per milliliter or higher at week 48 were found in 5 patients (1.6%) in the ER injectable therapy group and 3 patients (1.0%) in the oral therapy group (difference, 0.6% [95% confidence interval [CI], -1.1 to 2.4%]).[2] In analysis of the primary endpoint, non-inferiority of the ER injectable therapy was concluded if the upper limit of the CI for the difference between ER injectable therapy and oral therapy in the percentage of patients with an HIV-1 RN level of 50 copies per millimeter or higher at week 48 was less than 6 percentage points.[2] Thus, these results met the pre-specified noninferiority criterion for the primary endpoint.[2] The ER injectable therapy was also noninferior to oral therapy with respect to the key secondary endpoint of an HIV-1 RNA level of less than 50 copies per milliliter at week 48 (92.5% and 95.5%, respectively; adjusted difference, -3.0%; 95% CI, -6.7 to 0.7%), which met the pre-specified noninferiority criterion of 10 percentage points.[2] (Note that the sum of these endpoints in these studies do not equal 100% because virologic data were not available to some patients who withdrew from study early). No evidence of heterogeneity in these between-group differences was found across randomization strata or according to baseline patient characteristics.[2] Results were also consistent in the per-protocol population (HIV-1 RNA level ≥50 copies/mL, 1.4% for long-acting therapy vs. 1.0% for oral therapy, difference 0.3% [95% CI, -1.4 to 2.1%]).[2]

Patients in the ER injectable therapy group reported greater improvement from baseline in treatment satisfaction than patients in the oral therapy group, according to the HIVTSQs. The particular HIVTSQs used in this trial was a 12-item questionnaire with a total score range from 0 (very dissatisfied) to 66 (very

satisfied); both groups had a baseline HIVTSQs score of about 55 points. At 44 weeks, the adjusted mean increase in score from baseline was 5.68 points higher (95% CI, 4.37 to 6.98; p<0.001) in the long-acting therapy group than in the oral therapy group.[2]

Upon completion of the 52-week maintenance phase of the ATLAS trial, patients with plasma HIV-1 RNA less than 50 copies per milliliter in both the ER injectable therapy group and the oral therapy group had the option of continuing to participate in the extension phase of the trial, which was also funded by ViiV Healthcare and Janssen.[9] In this open-label, non-inferiority extension trial, 1,045 patients were randomized to cabotegravir 600 mg and rilpivirine 900 mg every 8 weeks or cabotegravir 400 mg and rilpivirine 600 mg every 4 weeks. The primary endpoint was the percentage of patients with HIV-1 RNA of 50 copies per milliliter or greater at 48 weeks, with a non-inferiority margin of 4 percentage points. The HIV-1 RNA results from the group which received cabotegravir and rilpivirine every 8 weeks was non-inferior to the group that received cabotegravir and rilpivirine every 4 weeks (HIV-1 RNA ≥50 copies/mL: 2% vs. 1%, respectively) with an adjusted treatment difference of 0.8 percentage points (95% CI, -0.6 to 2.2%). There were 8 cases (2%) of confirmed virologic failure (HIV-1 RNA ≥200 copies/mL) in 8-week group and 2 cases (<1%) of confirmed virologic failure in the 4-week group.[9]

The FLAIR trial was also a 48-week, randomized, multi-center, open-label, non-inferiority, parallel-group trial.[3] Eligible patients were adults 18 years of age or older who had not previously received ARV therapy and had a plasma HIV-1 RNA level of 1000 copies per milliliter or higher at screening.[3] Key pertinent details and analysis of the trial are presented in **Table 1**. Patients received oral induction therapy with a fixed-dose combination of 50 mg of dolutegravir, 600 mg of abacavir, and 300 mg of lamivudine once daily (or dolutegravir with a non-abacavir NRTI backbone) for 20 weeks to lower their viral load below 50 copies per milliliter.[3] Patients who achieved viral suppression with a plasma HIV-1 RNA level less than 50 copies per milliliter after 16 weeks of induction therapy were randomly assigned, in a 1-to-1 ratio, to either continue the current oral therapy during the maintenance phase or switch to ER injectable cabotegravir and rilpivirine for at least 100 weeks (but all primary and secondary endpoints were assessed at 48 weeks).[3] Patients in the ER injectable cabotegravir and rilpivirine group received oral lead-in therapy with 30 mg cabotegravir and 25 mg of rilpivirine once daily for 4 weeks to assess safety and adverse effects of the drugs before transitioning to ER injectable therapy.[3] At week 4, patients received a loading injection of 600 mg cabotegravir and 900 mg of rilpivirine administered into the gluteus muscle.[3] Maintenance injections of 400 mg of cabotegravir and 600 mg or rilpivirine were administered within a 21- to 28-day window, and bridging therapy with oral cabotegravir and rilpivirine was available for patients unable to attend a visit for their monthly injections.[3]

The primary and key secondary endpoints were the same as the ATLAS trial.[2,3] One minor difference was the use of the HIV Treatment Satisfaction Questionnaire, change version (HIVTSQc) in the FLAIR trial instead of the HIVTSQs (status version) used in the ATLAS trial.[2,3] The HIVTSQc evaluated patient satisfaction with *current* ARV therapy compared with induction therapy; total scores range from −33 (much less satisfied now) to 33 (much more satisfied now).[3] As with HIVTSQs, no minimal clinically important difference has been established for the HIVTSQc in patients with HIV-1 infection.[8]

For the primary endpoint, an HIV-1 RNA level of 50 copies per milliliter or higher at week 48 was found in 6 patients (2.1%) who received ER injectable therapy and in 7 patients (2.5%) who received oral therapy (difference of -0.4%; 95% CI, -2.8 to 2.1%), which met the pre-specified noninferiority criterion for the primary endpoint.[3] Similarly, ER injectable therapy was noninferior to oral therapy with regard to the key secondary end point of the percentage of patients with an HIV-1 RNA level of less than 50 copies per milliliter at week 48 (93.6% and 93.3%, respectively; difference of 0.4%; 95% CI, -3.7 to 4.4%), which met the pre-specified noninferiority criterion of 10 percentage points.[3] Results for the primary and key secondary endpoints were also consistent in the per-protocol population.[3] No evidence of heterogeneity in these between-group differences was found across randomization strata or according to other baseline characteristics.[3]

At week 48, the HIVTSQc total score for patient satisfaction with current treatment as compared with induction treatment was higher in the ER injectable therapy group than in the oral therapy group (adjusted mean difference, 4.1 points; 95% CI, 2.8 to 5.5 points).[3] No difference was found in the mean adjusted

HIVTSQs scores at week 44 between the two groups (0.7 points; 95% CI, -0.4 to 1.9 points; p=0.22).[8] Overall, a strong and consistent finding was not found for any of the quality of life outcomes across the ATLAS and FLAIR trials.[8]

Overall, the treatment groups in both phase 3 trials had comparable virologic responses.[2,3] The primary endpoint for both trials, defined as an HIV-1 RNA level greater than 50 copies per milliliter, was found in 1.6% and 1.0% of patients in the cabotegravir and rilpivirine and oral ARV regimens, respectively, of the ATLAS trial; the ARV-naïve patient population in the FLAIR trial found 2.1% and 2.5% of patients in the cabotegravir and rilpivirine and oral ARV regimens met the primary endpoint, respectively.[2,3] Based on a 6% noninferiority margin, the results demonstrated that ER injectable cabotegravir and rilpivirine was noninferior to continuation of oral ARV therapy, with between-group treatment differences of 0.6% (95% CI, -1.1 to 2.4%) in the ATLAS trial and -0.4% (95% CI, -2.8% to 2.1%) in the FLAIR trial.[2,3] Noninferiority for the primary endpoints was also observed in the per-protocol populations.[2,3] The proportion of patients with an HIV-1 RNA viral load less than 50 copies per milliliter at week 48 was 93% and 95% in the ER injectable cabotegravir and rilpivirine group and 94% and 93% in the oral ARV group in the ATLAS and FLAIR trials, respectively.[2,3] A few further considerations may be noted:

- None of the virologic outcomes showed a statistically significant difference by relevant subgroups (sex at birth, baseline HIV-1 RNA level, and CD4+ cell count).[2,3]
- Subgroup analyses showed virologic failure rates (HIV-1 RNA ≥50 copies/mL) were higher for the cabotegravir and rilpivirine groups versus the oral groups among females, higher baseline body mass index (BMI ≥30 kg/m^2) and females with a higher baseline BMI (BMI ≥30 kg/m^2).[1] Overall, 3 female subjects with higher baseline BMI had virologic failure in the pooled cabotegravir and rilpivirine groups, compared to none in the pooled control groups. These differences cannot be interpreted as statistically significant nor clinically relevant, but the FDA advised that the durability of a 2-drug regimen beyond 48 weeks to maintain virologic suppression remains unknown; therefore, additional evaluation for differences in outcome among these subgroups is warranted.[1]
- Limited data are available on the durability of a 2-drug regimen to maintain virologic suppression beyond 48 weeks.
- The open-label nature of the trials and lack of validation of a minimum clinically important difference for the HIVTSQ endpoints prohibit any conclusions for quality of life outcomes.
- Resistance to the study drugs occurred infrequently; 6 cases of treatment-emergent resistance to cabotegravir or rilpivirine were identified between the two trials.[2,3] The efficacy of ER injectable cabotegravir and rilpivirine is unknown among patients who have a baseline K103N substitution, acquired INSTI or NNRTI resistance, or with history of treatment failure.[1]
- Adherence to both injectable and oral regimens exceeded 90 percent with low attrition bias across studies.[2,3]
- Study investigators and authors were employees of the drug sponsors and performed statistical analyses and trial data interpretation.
- The U.S. Department of Health and Human Services HIV treatment guideline recently added ER injectable cabotegravir and rilpivirine as a recommended treatment option in adults currently on oral ARV therapy with documented viral suppression.[6]

It should also be noted that a supportive phase 2b trial was conducted which found that ER injectable cabotegravir and rilpivirine was as effective as a once daily three drug oral cabotegravir-based therapy in maintaining viral suppression in adult patients with HIV-1 infection not previously treated with ARV therapy in the Long-Acting antireTroviral Treatment Enabling (LATTE)-2 trial (NCT02120352).[10]

The LATTE-2 trial was a phase 2b, randomized, multi-center, open-label, non-inferiority trial that compared the efficacy and safety of ER injectable cabotegravir and rilpivirine, administered intramuscularly every 4 weeks or every 8 weeks, with that of oral cabotegravir plus abacavir-lamivudine, through 96 weeks for

patients who had achieved successful HIV-1 viral suppression with oral cabotegravir, abacavir and lamivudine during a 20-week induction period.[10] Key pertinent details and analysis of the trial are presented in **Table 1**.

Eligible patients who entered the induction period received a regimen of oral cabotegravir 30 mg, abacavir 600 mg and lamivudine 300 mg once daily for 20 weeks.[10] Rilpivirine 25 mg once daily was added 4 weeks before randomization (week 16 of the induction period) and continued until the first injection clinic visit (day 1 of maintenance phase).[10] Patients who tolerated the induction period regimen and achieved plasma HIV-1 RNA less than 50 copies per milliliter at week 16 of the induction period were eligible to enter the maintenance phase.[10] At day 1 of the 96-week maintenance phase, patients were randomly assigned to receive ER injection of cabotegravir 400 mg plus rilpivirine 600 mg (two 2 mL injections) every 4 weeks or cabotegravir 600 mg plus rilpivirine 900 mg (two 3 mL injections) every 8 weeks, or to continue receiving oral cabotegravir, abacavir and lamivudine once daily. Both 4-week and 8-week ER injectable regimens included an initial loading dose of cabotegravir 800 mg.[10]

The primary endpoints were the proportion of patients with HIV-1 RNA less than 50 copies per milliliter at week 32 of the maintenance phase and the proportion of patients with protocol-defined virologic failure (two consecutive plasma HIV-1 RNA measurements of ≥200 copies/mL).[10] Key secondary endpoints included the proportion of patients with plasma HIV-1 RNA less than 50 copies per milliliter at week 96.[10] In addition, treatment satisfaction was measured using the HIVTSQs, which was completed by patients at regular intervals throughout the study.[10] The study hypothesis for the primary endpoint that evaluated the proportion of patients with HIV-1 RNA less than 50 copies per milliliter at week 32 was that the injectable regimens were comparable to the oral regimen, defined as a proportion difference no greater than 10%.[10] A posterior probability of at least 90% was prespecified as the decision rule for claiming comparability for each comparison.[10]

At 32 weeks following randomization, both groups who received injectable dosing regimens met primary criteria for comparability in viral suppression relative to the oral comparator group.[10] Viral suppression was maintained at 32 weeks in 51 (96%) of 56 patients in the oral group, 108 (94%) of 115 patients in the 4-week group (difference 2.8% [-5.8% to 11.5%] vs. oral regimen), and 109 (95%) of 115 patients in the 8-week group (difference 3.7% [-4.8% to 12.2%] vs. oral regimen).[10] At week 96, viral suppression was maintained in 47 (84%) of 56 patients in the oral group, 100 (87%) of 115 patients in the 4-week group, and 108 (94%) of 115 patients in the 8-week group.[10] Three patients (1%) experienced protocol-defined virologic failure (two in the 8-week group; one in the oral treatment group).[10] At week 96, patients reported high levels of satisfaction on the HIVTSQs across all 3 groups, with 246 (97%) of 254 patients selecting a score of 5 or 6 on a 6-point version of this satisfaction scale.[10] A similar percentage of patients in each injectable group (99/100 in the 4-week group and 107/108 in the 8-week group) reported they would be highly satisfied to continue their current regimen, while a lower percentage would elect to continue on oral dosing (78%; 36 of 46 patients in the oral treatment group).[10] In a post-hoc analysis, patients in the 4-week, 8-week and oral treatment groups reported a median HIVTSQs total score of 63.5, 65.0 and 60.0 at week 96 (post hoc $p<0.001$).[7] Selection and performance biases were introduced with these patient satisfaction outcomes, however, because patients who discontinued the study for any reason before week 96 did not complete the questionnaire at this timepoint.[10]

Clinical Safety:

In the ATLAS trial, 95% of patients in the ER injectable cabotegravir and rilpivirine group and 71% of patients in the oral group reported at least one adverse event (see **Table 1**).[2] The differences could be attributed to injection-site reactions, which occurred in 83% of patients in the injection group.[2] Among the patients who received ER injection therapy, 99% of injection-site reactions were of mild or moderate severity; no life-threatening or fatal (grade 4 or 5) reactions were reported, and 88% of reactions resolved within 7 days (median, 3 days).[2] The most common injection-site reaction was pain (75%); nodule (12%), induration (10%), and swelling (7%) were less common.[2] Injection-site reactions occurred in 69% of patients after the initial 3-mL injections at week 4; frequencies of these reactions declined progressively after the subsequent 2-mL injections, declining to 11% at week 48.[2] At week 48, the median weight gains

were 1.80 kg (interquartile range, -0.30 to 4.90 kg) in the ER injection group and 0.30 kg (interquartile range, -1.60 to 2.50 kg) in the oral group.[2] Five patients in the ER injection group and one patient in the oral group had alanine aminotransferase elevations to at least 3-times the upper limit of the normal range.[2] Among the patients who had these events, newly diagnosed hepatitis A was declared in 3 patients, hepatitis B in one patient, and hepatitis C in one patient.[2]

In the FLAIR trial, 86% of patients had at least one injection-site reaction in the ER injection group (see **Table 1**).[3] The most common injection-site reaction was pain, which was reported by 82% who received at least one injection.[3] Most of the injection-site pain events were mild (86%) or moderate (13%) severity; less than 1% were severe (grade 3), and there were no grade 4 adverse events.[3] The incidence of injection-site reactions was highest (71%) after the initial 3-mL injections at week 4 and subsequently decreased to 20% at week 48.[3] The median duration of injection-site reactions was 3 days; 88% of cases resolved within 7 days.[3]

The most common adverse events in the ER injection group, excluding injection-site reactions, were nasopharyngitis, headache and upper respiratory tract infection (see **Table 1**).[3] Overall, drug-related adverse events exclusive of injection-site reactions in the FLAIR trial were more common with ER injection group (28%) than oral group (10%).[3] Serious adverse events occurred in 18 patients (6%) who received ER injection therapy and 12 patients (4%) who received oral therapy, with no deaths.[3] Adverse events that led to early withdrawal from the trial occurred in 9 patients (3%) in the ER injection group and in 4 patients (1%) in the oral group.[3] In the ER injection group, the only events that led to withdrawal in more than 1 patient were viral hepatitis and injection-site pain (in 5 and 2 participants, respectively).[3] During the maintenance phase, 7 patients (2%) who received long-acting therapy and in 2 patients (1%) who received oral therapy were removed from the trial due to liver-related events, including 8 cases of acute viral hepatitis.[3] At week 48 of the FLAIR trial, the median weight gain from baseline was 1.3 kg (interquartile range, −1.0 to 5.0 kg) in the ER injection group and 1.5 kg (interquartile range, −1.0 to 3.9 kg) in the oral group.

In the LATTE-2 trial, total adverse events of any grade and attribution occurred in 115 (100%) patients in the 4-week group, 115 (100%) in the 8-week group, and 54 (96%) in the oral treatment group (see **Table 1**).[10] Injection-site pain, the most common injection-site reaction, was the most frequently reported adverse event in the injection groups (112 [97%] patients in the 4-week group, 110 [96%] patients in the 8-week group).[10] Most injection-site reactions were mild (grade 1; 3648 [84%] of 4360 injections) or moderate (grade 2; 673 [15%] of 4360 injections) in intensity, with median symptom duration of 3 days.[10] Serious adverse events occurred in 13 (11%) patients in each of the injection groups and nine (16%) patients in the oral group, only one of which was drug related (migraine, which occurred in the initial oral induction period of the study).[10] Serious adverse events occurred in 11 (10%) patients in each of the injection groups compared with 7 patients (13%) in the oral group.[10] However, none was considered to be related to study treatment.[10]

Resistance analyses were also performed in each trial. Three patients in the ER injection group who experienced virologic failure in the ATLAS trial were found to have rilpivirine resistance-associated reverse-transcriptase mutations upon examination of HIV-1 RNA samples; an integrase mutation N155H was also detected one of these 3 patients.[2] These mutations reduced susceptibility to rilpivirine by a factor of 6.5, and cabotegravir susceptibility was reduced by a factor of 2.7 in the patient with N155H.[2] Two patients with virologic failure in the ATLAS trial also had an identified L74I integrase polymorphism at baseline, but the investigators concluded that this mutation by itself is not known to decrease susceptibility to INSTIs.[2] No patient with virologic failure missed an injection or received injections outside the permitted window.[2] In the FLAIR trial, 3 patients had NNRTI and INSTI resistance mutations that developed during ER injection therapy; these mutations reduced susceptibility to rilpivirine in 2 patients by a factor of more than 2 and reduced susceptibility to cabotegravir in all 3 patients by a factor of more than 5.[3] These 3 patients had HIV-1 subtype A1 with the L741 integrase polymorphism at baseline.[3] However, 51 of the 54 patients in the ER injection group who had HIV-1 with the L741 integrase polymorphism at baseline did not have virologic failure.[3] In subgroup analyses of the primary endpoint, no statistically significant difference between treatments was observed in subgroups defined according to the presence or absence of the L74I integrase polymorphism.[3] In the LATTE-2 trial, 3 patients (two in the 8-week group, [week 4 and week 48], one in the oral treatment group [week 8]) met the criteria for

protocol-defined virological failure through 96 weeks.[10] No treatment-emergent resistance mutations in the genes encoding viral reverse transcriptase, protease, or integrase were identified in the patient in the oral treatment group.[10] Of the two patients in the 8-week group, a mixture emerged for one at integrase codon 269 (R269R/G), which did not decrease cabotegravir susceptibility; however one of these patient had treatment-emergent reverse transcriptase mutations K103N, E138G, and K238T, with phenotypic resistance to efavirenz, rilpivirine, and nevirapine, and an integrase mutation Q148R, with phenotypic resistance to raltegravir, elvitegravir, and cabotegravir, while remaining sensitive to dolutegravir.[10]

In summary, the proportion of patients in the ER injectable cabotegravir and rilpivirine who experienced adverse effects was greater than in the oral group. This difference was partly attributable to various injection site reactions. Injection site pain was the most commonly reported injection site reaction, which occurred in 75% and 90% of patients in the phase 3 trials, followed by injection site nodule and injection site induration.[2,3] No injection site reactions were reported as serious adverse events and early study withdrawal due to injection site reactions was low.[2,3] Exclusive of injection site reactions, the most frequent adverse events in the phase 3 trials were nasopharyngitis, headache, upper respiratory tract infection and diarrhea.[2,3] Moderate weight gain (median, 1.5 and 1.8 kg) was also noted.[2,3] Additional long-term follow-up data are anticipated to further assess cardiovascular or metabolic risks associated with weight gain.[1] The incidence of nonfatal serious adverse events was low across phase 3 trials (5% to 6%) but higher in the phase 2b trial.[2,3,10] The most serious adverse events included depressive disorders, hypersensitivity reaction and hepatotoxicity, which are associated with other INSTIs and NNRTIs, and are adequately labeled in the product prescribing information.[1,4,5] Overall, there were no deaths attributable to the study drugs.[2,3,10] Emergence of resistance to both cabotegrair and rilpivirine occurred more frequently among virologic failures in the trials and also at a higher rate than in the oral groups.[2,3,10]

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) HIV-1 RNA suppression
2) Virologic failure
3) Drug resistance
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) HIV-1 RNA levels ≥50 copies/mL at 48 weeks

Table 1. Comparative Evidence Table for Extended-release Cabotegravir and Rilpivirine.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Swindells, et al. (ATLAS)[2] Phase 3 OL, MC, PG, NI, RCT 52 weeks	1. Oral CAB 30 mg + RPV 25 mg x4 weeks; eligible patients then received long-acting CAB 600 mg + RPV 900 mg IM, followed by CAB 400 mg + RPV 600 mg IM every 4 weeks x total 52 weeks 2. Patients continued baseline NNRTI-, INSTI or PI-based oral therapy 1:1	Demographics: -Age (median): 42 y (18-62 y) -Male: 77% -White: 68% -Black: 23% -Asian: 6% -CD4+ ≥500 cells/mm^3: 74% -Baseline ARV: ▪ 2x NRTIs +NNRTI: 50% ▪ 2x NRTIs +INSTI: 33% ▪ 2x NRTIs +PI: 17%. -Current ARV median duration: 4.3 y Key Inclusion Criteria: -HIV-1 infection -Age ≥18 y -Receiving ARV regimen w/o virologic failure -No Δ in ARV regimen in past 6 months -HIV-1 RNA <50 copies/mL Key Exclusion Criteria: -HBV -h/o virologic failure -INSTI or NNRTI resistance mutations	ITT: 1. 308 2. 308 PP: 1. 294 2. 292 Attrition: 1. 26 2. 18	Primary Endpoint % w/ plasma HIV-1 RNA levels ≥50 copies/mL at week 48: 1. 1.6% 2. 1.0% Difference, 0.6% (95% CI, -1.1 to 2.4%) Key Secondary Endpoints: % w/ plasma HIV-1 RNA levels <50 copies/mL at week 48: 1. 92.5% 2. 95.5% Difference, -3.0% (95% CI, -6.7 to 0.7%) Confirmed Virologic Failure (2 consecutive plasma HIV-1 RNA measurements ≥200 copies/mL: 1. n=3 2. n=4 No statistical analysis HIVTSQ, adjusted mean difference from baseline: Week 24: 1. 6.43 (95% CI, 5.59-7.28) 2. 1.05 (95% CI, 0.81-1.91) Week 44: 1. 6.12 (95% CI, 5.21-7.03) 2. 0.44 (95% CI, -0.48-1.37) Adjusted difference at week 44: 5.68 points (95% CI, 4.37 to 6.98)	NA NA NA NA	Any AE: 1. 95% 2. 71% Any AE, excluding inj-site reactions: 1. 86% 2. 71% Grade 3 or 4 events: 1. 11% 2. 7% SAE: 1. 4% 2. 5% AE leading to study withdrawal: 1. 5% 2. 2% Inj Site Pain: 75% Inj Site Nodule: 12% Median Wt Gain: 1. 1.8 kg 2. 0.3 kg Nasopharyngitis: 1. 17% 2. 14% Headache: 1. 10% 2. 8% Upper Respiratory Tract Infection: 1. 12% 2. 6%	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (unclear) method of randomization unclear; randomization stratified by backbone agent in baseline ARV regimen (PI, INSTI, or NNRTI) and sex at birth. Performance Bias: (high) open label. Detection Bias: (high) open label; data analyzed by mITT (participants who received ≥1 dose). Results were consistent in PP population, which excluded 30 patients for protocol deviations. Attrition Bias: (low) 93% of patients completed 52-week maintenance phase; 8% in long-acting and 6% in oral therapy groups withdrew from trial early. Reporting Bias: (low) endpoints reported as described. Other Bias: (high) authors were employees of ViiV Healthcare and GSK performed statistical analyses and data interpretation. **Applicability**: Patient: participants representative sample of HIV-1 positive population; nearly all patients randomized to CAB+RPV met eligibility criteria with oral lead-in period based on tolerability before transitioning to IM. Intervention: dosing aligns with FDA approved regimen. Only 2% used oral CAB+RPV bridge (4-29 days) in the trial to cover missed or delayed inj visits. Comparator: baseline oral ARV regimen was stable and successfully managed condition during maintenance phase. Outcomes: NI concluded if upper limit of 95% CI in primary endpoint was <6%; justification was unclear but upper limit found increases confidence of NI. Note that the sum of these endpoints in these studies do not equal 100% because virologic data were not available to some patients who withdrew from study early. Setting: 115 sites in 13 countries.

2. Orkin, et al. (FLAIR)[3] Phase 3 OL, MC, PG, NI, RCT 52 weeks	1. Oral CAB 30 mg + RPV 25 mg x4 weeks; eligible patients then received long-acting CAB 600 mg + RPV 900 mg IM, followed by CAB 400 mg + RPV 600 mg IM every 21-28 days x total 52 weeks 2. DTG/ABC/3TC 50/600/300 mg PO daily 1:1	Demographics: -Age (median): 34 y -Male: 88% -White: 74% -Black: 18% -HIV-1 RNA ≥100,000 copies/mL: 20% -CD4+ ≥350 cells/mm^3: 69% (90% by start of maintenance phase) Key Inclusion Criteria: -HIV-1 positive -Age ≥18 y -ARV-naïve Key Exclusion Criteria: -Stage 3 HIV -HBV -NNRTI resistance mutations other than the K103N mutation -Moderate or severe hepatic function	ITT: 1. 283 2. 283 PP: 1. 278 2. 282 Attrition: 1. 25 2. 22	Primary Endpoint: % w/ plasma HIV-1 RNA levels ≥50 copies/mL at week 48: 1. 2.1% 2. 2.5% Difference, -0.4% (95% CI, -2.8% to 2.1%) Key Secondary Endpoints: % w/ plasma HIV-1 RNA levels <50 copies/mL at week 48: 1. 93.6% 2. 93.3% Difference, 0.4% (95% CI, -3.7% to 4.4%) Confirmed Virologic Failure (2 consecutive plasma HIV-1 RNA measurements ≥200 copies/mL: 1. n=4 2. n=3 No statistical analysis HIVTSQc, mean difference from baseline at Week 48: 1. 29.6 (SE 0.49) 2. 25.5 (SE 0.48) Adjusted mean difference: 4.1 points (95% CI, 2.8 to 5.5; p<0.001)	NA NA NA NA	Any AE: 1. 94% 2. 80% Any AE, excluding inj-site reactions: 1. 87% 2. 80% Grade 3 or 4 events: 1. 11% 2. 4% SAE: 1. 6% 2. 4% AE leading to study withdrawal: 1. 3% 2. 1% Inj Site Pain: 1. 90% Median Wt Gain: 1. 1.3 kg 2. 1.5 kg Nasopharyngitis: 1. 20% 2. 17% Headache: 1. 14% 2. 7% Upper Respiratory Tract Infection: 1. 13% 2. 10%	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) central randomization sequence generated by software that performed blocks shared across sites and stratified by baseline HIV-1 RNA level (<100,00 or ≥100,000 copies/mL) and sex at birth. Performance Bias: (high) open label. Detection Bias: (high) open label; data analyzed by mITT (participants who received ≥1 dose). Results were consistent in PP population, which excluded patients who had protocol deviations that were likely to affect efficacy assessments or lead to discontinuation of the trial drugs. Attrition Bias: (low) 98% of the 3577 expected inj visits (12 per patient by week 48) occurred in 21-35 day window from prev inj. Patient-reported adherence in oral-therapy group >90%. Reporting Bias: (low) endpoints reported as described. Other Bias: (high) Trial funded by ViiV Healthcare and Janssen which participated in design of trial and in analysis and interpretation of data. **Applicability**: Patient: participants representative sample of HIV-1 positive, ARV-naïve population; mostly younger white males. Intervention: Dosing and bridging used in trial approved and marketed in U.S. Comparator: recommended oral ARV regimen used with DTG/ABC/3TC. DTG + 2 NRTIs other than ABC permitted if adverse effects from DTG/ABC/3TC. Outcomes: NI concluded if upper limit of 95% CI for the difference in the primary endpoint was <6%; this was based on assumed 2% virologic failure rate in the oral therapy group and a treatment difference of <3% between the groups. No significant differences between treatments across randomization strata or baseline characteristics. Setting: 108 sites in 11 countries.

3. Margolis, et al. (LATTE-2)[10] Phase 2b OL, MC, PG, NI, RCT 20 week oral induction phase 96 week maintenance phase	1. long-acting CAB 400 mg + RPV 600 mg IM every 4 weeks 2. long-acting CAB 600 mg + RPV 900 mg IM every 8 weeks 3. Cabotegravir 30 mg and ABC/3TC 600/300 mg PO once daily 2:2:1	Demographics: -Age (median): 35 y -Male: 92% -White: 79% -Black: 15% -HIV-1 RNA >100,000 copies/mL: 18% -Median CD4+ 489 cells/mm^3 -Hep C: 3% Key Inclusion Criteria: -HIV-1 positive -Age ≥18 y - ≤10 days of previous ARV tx -HIV-1 RNA ≥1000 copies/mL -CD4+ ≥200 cells/mm^3 Key Exclusion Criteria: -HBV -Any major ARV resistance mutation -Moderate or severe hepatic function -Clinically relevant hepatitis -CrCl <50 mL/min -Chronic anticoagulant	ITT: 1. 115 2. 115 3. 56 PP: 1. 2. 3. Attrition: 1. 14 2. 5 3. 9	Primary Endpoints: % w/ plasma HIV-1 RNA levels <50 copies/mL at week 32: 1. 108 (94%) 2. 109 (95%) 3. 51 (91%) Difference vs. Oral: 1 vs. 3: 2.8% (95% CI, -5.8% to 11.5%) 2 vs. 3: 3.7% (95% CI, -4.8% to 12.2%) *Posterior probability for comparability met threshold at >90%.* Confirmed Virologic Failure (2 consecutive plasma HIV-1 RNA measurements ≥200 copies/mL: 1. 0 2. 2 3. 1 Key Secondary Endpoints: % w/ plasma HIV-1 RNA levels <50 copies/mL at week 96: 1. 100 (87%) 2. 108 (95%) 3. 47 (84%) Difference vs. Oral: 1 vs. 3: 3.0% (95% CI, -8.4% to 14.4%) 2 vs. 3: 10.0% (95% CI, -0.6% to 20.5%)		Any AE: 1. 100% 2. 100% 3. 96% SAE: 1. 11% 2. 11% 3. 16% Study Withdrawal from AE: 1. 7% 2. 2% 3. 2% Inj Site Pain: 1. 97% 2. 96% 3. NA Mild [Grade 1]: 84% Mod [Grade 2]: 15% Nasopharyngitis: 1. 34% 2. 30% 3. 39% Diarrhea: 1. 28% 2. 23% 3. 205 Headache: 1. 23% 2. 25% 3. 25%		**Risk of Bias (low/high/unclear)**: Selection Bias: (low) central randomization sequence generated by software that performed blocks shared across sites and stratified by baseline HIV-1 RNA level (<50 or ≥50 copies/mL). Performance Bias: (high) open label. Detection Bias: (high) open label; data analyzed by mITT (participants who received ≥1 dose). PP sensitivity analyses excluding patients with prespecified protocol deviations were not done as fewer than 5% had such deviations (threshold for conducting analysis specified in advance in the analysis plan). Posterior probability for comparability for each hypothesis confirmed if it was >90% for the primary endpoint. Q4W vs. oral =99%; Q8W vs. oral =100%; Q8W vs. Q4W =99.9%, confirming NI. Attrition Bias: (low) 21/309 (7%) failed induction phase in the mITT population. Of these, 5 were for lack of efficacy, 3 for AE, 3 met predefined liver chemistry stopping criteria (others withdrew consent, had protocol deviations, were lost to follow-up). 286 entered maintenance phase. Reporting Bias: (high) multiple primary endpoints reported without clear method of statistical analysis and hierarchy. Several endpoints reported similar to exploratory outcomes without statistical analysis. Other Bias: (high) Study funded by ViiV Healthcare and Janssen. The funders participated in the study design, data gathering, analysis, and interpretation. **Applicability**: Patient: ARV-naïve patients; mostly younger white males. Intervention: Q4W dosing regimen (group 1) approved and marketed in U.S. Comparator: Recommended oral ARV regimen used INSTI + 2 NRTIs. Outcomes: Endpoints demonstrate virologic suppression for treatment, with no significant differences between treatments during the

								trial. Primary endpoint met study threshold for comparability. Week 96 virologic suppression outcomes were: 87% (4-week grp), 94% (8-week grp), 84% (oral grp) Setting: 50 sites in the USA, Canada, Spain, France, and Germany.

Abbreviations: 3TC = lamivudine; ABC = abacavir; ARR = absolute risk reduction; ARV = antiretroviral; CAB = cabotegravir; CI = confidence interval; CrCl = creatinine clearance; DTG = dolutegravir; GSK = GlaxoSmithKline; HBV = Hepatitis B virus; HIVTSQ = 12-item HIV Treatment Satisfaction Questionnaire, status version (total score ranges from 0 (very dissatisfied) to 66 (very satisfied); HIVTSQc = HIV Treatment Satisfaction Questionnaire, change version (total score ranges from -33 (much less satisfied now) to 33 (much more satisfied now); HIV = human immunodeficiency virus; h/o = history of; IM = intramuscular; INSTI = integrase strand-transfer inhibitor; ITT = intention to treat; MC = multi-center; MCID = minimum clinically important difference; mITT = modified intention to treat; mL = milliliter; N = number of subjects; NA = not applicable; NI = non-inferiority; NNH = number needed to harm; NNRTI = nonnucleoside reverse-transcriptase inhibitor; NNT = number needed to treat; NRTI = nucleoside or nucleotide reverse-transcriptase inhibitor; OL = open label; PG = parallel group; PI = protease inhibitor (boosted); PP = per protocol; RCT = randomized controlled trial; RNA = ribonucleic acid; RPV = rilpivirine; SAE = serious adverse event; w/i = within; w/o = without; y = years.

The pharmacology and pharmacokinetic properties of ER injectable cabotegravir and rilpivirine are described in **Table 2**.

Table 2. Pharmacology and Pharmacokinetic Properties of Extended-release Injectable Cabotegravir and Rilpivirine.[4]

Parameter	Cabotegravir	Rilpivirine
Mechanism of Action	INSTI	NNRTI
Oral Bioavailability	n/a	n/a
Distribution and Protein Binding	T_{max} = 7 days Bound to plasma proteins: >99.8%	T_{max} = 3-4 days Bound to plasma proteins: 99.7%
Elimination	Total dose excreted in urine: 27% Dose excreted unchanged in urine: 0% Total dose excreted in feces: 59% Dose excreted unchanged in feces: 47%	Total dose excreted in urine: 6% Dose excreted unchanged in urine: <1% Total dose excreted in feces: 85% Dose excreted unchanged in feces: 26%
Half-Life	$T_{1/2}$ (weeks): 5.6 to 11.5	$T_{1/2}$ (weeks): 13 to 28
Metabolism	UGT1A1 UGT1A9 (minor)	CYP3A

Abbreviations: AUC = area under the plasma concentration-time curve; C_{max} = maximum plasma concentration; CYP3A = cytochrome P450 3A; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; $T_{1/2}$ = half-life; T_{max} = time to maximum plasma concentration; UGT1A1 = UDP glucuronosyltransferase 1 family, polypeptide A1; UGT1A9 = UDP glucuronosyltransferase 1 family, polypeptide A9.

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

VOCABRIA (cabotegravir) tablets, for oral use
Initial U.S. Approval: 2021

INDICATIONS AND USAGE

VOCABRIA is a human immunodeficiency virus type-1 (HIV-1) integrase strand transfer inhibitor (INSTI) indicated in combination with EDURANT (rilpivirine) for short-term treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine, for use as:

- oral lead-in to assess the tolerability of cabotegravir prior to administration of CABENUVA (cabotegravir; rilpivirine) extended-release injectable suspensions. (1)
- oral therapy for patients who will miss planned injection dosing with CABENUVA. (1)

DOSAGE AND ADMINISTRATION

- One tablet of VOCABRIA 30 mg taken orally once daily for approximately 1 month in combination with one tablet of EDURANT (rilpivirine) 25 mg taken orally once daily with a meal. (2.1)

DOSAGE FORMS AND STRENGTHS

- Tablets: 30 mg (3)

CONTRAINDICATIONS

- Previous hypersensitivity reaction to cabotegravir. (4)
- Coadministration with carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifampin, and rifapentine. (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity reactions have been reported in association with other integrase inhibitors. Discontinue VOCABRIA immediately if signs or symptoms of hypersensitivity reactions develop. (5.1)
- Hepatotoxicity has been reported in patients receiving cabotegravir. Monitoring of liver chemistries is recommended. Discontinue VOCABRIA if hepatotoxicity is suspected. (5.2)
- Depressive disorders have been reported with VOCABRIA. Prompt evaluation is recommended for depressive symptoms. (5.3)
- Risks Associated with Combination Treatment: Review the prescribing information for EDURANT for information on rilpivirine prior to initiation of VOCABRIA in combination with EDURANT. (5.5)

ADVERSE REACTIONS

The most common adverse reactions (Grades 1 to 4) observed in at least 3 subjects receiving VOCABRIA were headache, nausea, abnormal dreams, anxiety, and insomnia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact ViiV Healthcare at 1-877-844-8872 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Refer to the full prescribing information for important drug interactions with VOCABRIA. (4, 5.4, 7)
- Because VOCABRIA in combination with EDURANT (rilpivirine) is a complete regimen, coadministration with other antiretroviral medications for the treatment of HIV-1 infection is not recommended. (7.1)
- Drugs that induce uridine diphosphate glucuronosyltransferase (UGT)1A1 may decrease the plasma concentrations of cabotegravir. (4, 7.2, 7.3)

USE IN SPECIFIC POPULATIONS

- Lactation: Breastfeeding is not recommended due to the potential for HIV-1 transmission. (8.2)

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

Revised: 1/2021

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

CABENUVA (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension), co-packaged for intramuscular use
Initial U.S. Approval: 2021

INDICATIONS AND USAGE

CABENUVA, a 2-drug co-packaged product of cabotegravir, a human immunodeficiency virus type-1 (HIV-1) integrase strand transfer inhibitor (INSTI), and rilpivirine, an HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI), is indicated as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine. (1)

DOSAGE AND ADMINISTRATION

- Prior to initiating treatment with CABENUVA, oral lead-in dosing should be used for approximately 1 month to assess the tolerability of cabotegravir and rilpivirine. (2.2)
- For intramuscular (IM) gluteal injection only. (2.3, 2.5)
- Recommended Dosing Schedule: Initiate injections of CABENUVA (600 mg of cabotegravir and 900 mg of rilpivirine) on the last day of oral lead-in and continue with injections of CABENUVA (400 mg of cabotegravir and 600 mg of rilpivirine) every month thereafter. (2.3)

DOSAGE FORMS AND STRENGTHS

Cabotegravir extended-release injectable suspension and rilpivirine extended-release injectable suspension, co-packaged as follows: (3)
CABENUVA 400-mg/600-mg Kit:
- single-dose vial of 400 mg/2 mL (200 mg/mL) cabotegravir
- single-dose vial of 600 mg/2 mL (300 mg/mL) rilpivirine

CABENUVA 600-mg/900-mg Kit:
- single-dose vial of 600 mg/3 mL (200 mg/mL) cabotegravir
- single-dose vial of 900 mg/3 mL (300 mg/mL) rilpivirine

CONTRAINDICATIONS

- Previous hypersensitivity reaction to cabotegravir or rilpivirine. (4)
- Coadministration with drugs where significant decreases in cabotegravir and/or rilpivirine plasma concentrations may occur, which may result in loss of virologic response. (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity reactions have been reported with rilpivirine-containing regimens and in association with other integrase inhibitors. Discontinue CABENUVA immediately if signs or symptoms of hypersensitivity reactions develop. (5.1)
- Serious post-injection reactions with rilpivirine were reported. Monitor and treat as clinically indicated. (5.2)
- Hepatotoxicity has been reported in patients receiving cabotegravir or rilpivirine. Monitoring of liver chemistries is recommended. Discontinue CABENUVA if hepatotoxicity is suspected. (5.3)
- Depressive disorders have been reported with CABENUVA. Immediate medical evaluation is recommended for depressive symptoms. (5.4)
- Residual concentrations of cabotegravir and rilpivirine may remain in the systemic circulation of patients up to 12 months or longer. It is essential to initiate an alternative, fully suppressive antiretroviral regimen no later than 1 month after the final injection doses of CABENUVA. If virologic failure is suspected, prescribe an alternative regimen as soon as possible. (5.6)

ADVERSE REACTIONS

The most common adverse reactions (Grades 1 to 4) observed in ≥2% of subjects receiving CABENUVA were injection site reactions, pyrexia, fatigue, headache, musculoskeletal pain, nausea, sleep disorders, dizziness, and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact ViiV Healthcare at 1-877-844-8872 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Refer to the full prescribing information for important drug interactions with CABENUVA. (4, 5.5, 7)
- Because CABENUVA is a complete regimen, coadministration with other antiretroviral medications for the treatment of HIV-1 infection is not recommended. (7.1)
- Drugs that induce uridine diphosphate glucuronosyltransferase (UGT)1A1 or cytochrome P450 (CYP)3A4 may decrease the plasma concentrations of the components of CABENUVA. (4, 7.3, 7.4)
- CABENUVA should be used with caution in combination with drugs with a known risk of Torsade de Pointes. (7.3)

USE IN SPECIFIC POPULATIONS

- Pregnancy: After oral use of rilpivirine, exposures were generally lower during pregnancy compared with the postpartum period. (8.1)
- Lactation: Breastfeeding is not recommended due to the potential for HIV-1 transmission. (8.2)

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

Revised: 1/2021