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, May 23 2019 1:00 - 5:00 PM
DXC Conference Room
4070 27th Ct. SE
Salem, OR 97302
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 as required by 414.325(9).

	I. CALL TO ORDER	
1:00 PM	A. Roll Call & Introductions	R. Citron (OSU)
	B. Conflict of Interest Declaration	R. Citron (OSU)
	C. Approval of Agenda and Minutes	R. Citron (OSU)
	D. Department Update	T. Douglass (OHA)
	E. Legislative Update	T. Douglass (OHA)
1:15 PM	II. CONSENT AGENDA TOPICS	Chair
	A. Quarterly Utilization Reports	
	III. DUR ACTIVITIES	
1:20 PM	A. ProDUR Report	R. Holsapple (DXC)
	B. RetroDUR Report	D. Engen (OSU)
	C. Oregon State Drug Reviews	K. Sentena (OSU)
	1. 2017-2018 Year in Review: Important Safety Updates	
	2. Benzodiazepine Safety and Tapering	
	IV. DUR OLD BUSINESS	
1:35 PM	A. GnRH Modifiers	R. Citron (OSU)
	1. Designation of PDL status	
	2. Public Comment	
	3. Discussion of Clinical Recommendations to OHA	

1:40 PM	B. Combination Biologic Therapy Drug Use Evaluation 1. Drug Use Evaluation/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	S. Servid (OSU)
	V. DUR NEW BUSINESS	
1:50 PM	A. Attention Deficit Hyperactivity Disorder Drug Use Evaluation 1. Drug Use Evaluation/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	J. Ayoub (OSU)
2:10 PM	B. Adherence Monitoring in Schizophrenia Patients 1. Retrospective DUR Policy Proposal 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	S. Servid (OSU)
	VI. PREFERRED DRUG LIST NEW BUSINESS	
2:25 PM	A. Asthma/COPD Class Update and New Drug Evaluation 1. Class Update/Prior Authorization Criteria 2. Yupelri™ (revefenacin) New Drug Evaluation 3. Public Comment 4. Discussion of Clinical Recommendations to OHA	K. Sentena (OSU)
2:45 PM	B. Migraine Treatment and Prevention DERP Summary 1. DERP Summary/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	K. Sentena (OSU)
3:00 PM	BREAK	
3:10 PM	C. CGRP Inhibitors DERP Summary 1. DERP Summary/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	D. Engen (OSU)
3:25 PM	D. Potassium Exchangers Class Update and New Drug Evaluation 1. Class Update/Prior Authorization Criteria 2. Lokelma™ (sodium zirconium cyclosilicate) New Drug Evaluation 3. Public Comment 4. Discussion of Clinical Recommendations to OHA	D. Moretz (OSU)

3:45 PM	E. Other Dyslipidemia Drugs Class Update 1. Class Update/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	M. Herink (OSU)
4:05 PM	VII. EXECUTIVE SESSION	
4:50 PM	VIII. RECONVENE for PUBLIC RECOMMENDATIONS	
	IX. ADJOURN	

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Oregon Pharmacy and Therapeutics Committee – Appointed members

Name	Title	Profession	Location	Term Expiration
Kelley Burnett, DO	Physician	Pediatrician / Associate Medical Director	Grants Pass	December 2019
Dave Pass, MD	Physician	Medical Director	West Linn	December 2019
Stacy Ramirez, PharmD	Pharmacist	Ambulatory Care Pharmacist	Corvallis	December 2019
Tracy Klein, PhD, FNP	Public	Nurse Practitioner	Portland	December 2020
Caryn Mickelson, PharmD	Pharmacist	Pharmacy Director	Coos Bay	December 2020
William Origer, MD	Physician	Residency Faculty	Albany	December 2020
James Slater, PharmD	Pharmacist	Pharmacy Director	Beaverton	December 2020
Mark Helm, MD, MBA, FAAP	Physician	Pediatrician	Salem	December 2021
Russell Huffman, DNP, PMHNP	Public	Mental Health Nurse Practitioner	Salem	December 2021
Jim Rickards, MD, MBA	Physician	Radiologist / Medical Director	McMinnville	December 2021
Cathy Zehrung, RPh	Pharmacist	Pharmacy Manager	Silverton	December 2021

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, March 21, 2019
1:00 p.m. – 5:00 p.m.
DXC Building, 4070 27th Ct
Salem, OR 97301

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 as required by 414.325(9).

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

Members Present by Phone: Kelley Burnett, DO; Dave Pass, MD

Staff Present: Roger Citron, RPh; Sarah Servid, PharmD; David Engen, PharmD, CGP; Deanna Moretz, PharmD, BCPS; Kara Shirley, PharmD, BCACP, BCPS, BCPP; Richard Holsapple, RPh Dee Weston; Jennifer Torkelson; Brandon Wells; Jonnaliz Corbett; Trevor Douglass, DC, MPH

Staff Present by Phone: Kathy Sentena, PharmD

Audience: Tim McFerron, Alkermes; *Paul Thompson, Alkermes; Georgette Dzwilewski, Indivior; Joelle Ayoub, OHSU; *Mark Kohn, Novo Nordisk; *Kyle Gunter, Paratek; Erick Shoffe, Paratek; Trey Davenhill, Oregon State University; Sean Privette, Pacific University; Lisa Boyle, WVP Health; Bobbi Jo Duim, BMS; Dana Sox, AMAG; *Lisa Wells, Greenwich Biosciences; Tracey Larrah, AMAG; Keri Smith, Viiv; Trent Taylor, J&J, *Stephanie Yamamoto, J&J; Doug Buriani, Sobi; Troy Pendergraft, Tandem Diabetes Care; Chris Tanaka, Dexcom; *Margaret Olmon, AbbVie; Jeana Colabianchi, Sunovion; Danielle Shannon, WVP Health; *Keith Cheng, MHCAG; *George Fussell, MHCAG; Heidi Memmott, Takeda; Laura Jeffcoat, AbbVie

*Provided public testimony

Written testimony provided: Posted to OSU Website

I. CALL TO ORDER

A. The meeting was called to order at approximately 1:05 pm. Introductions were made by Committee members and staff.
B. No new conflicts of interest were declared.
C. Approval of agenda and January 2019 minutes presented by Mr. Citron.
ACTION: Motion to approve, 2nd, all in favor
D. Department Update: Trevor Douglass reviewed staffing changes.
E. Legislative Update: Trevor Douglass reviewed agency policy during legislative session regarding discussion of active bills. Reviewed: HB2678, SB138, HB2692, HB3093, SB872, HB 2689, HB 2680, and HB 2679.

II. CONSENT AGENDA TOPICS

A. GLP-1 Receptor Agonists Literature Scan
Recommendation:
- Make no changes to the PMPDP based on clinical evidence.
- Evaluate comparative drug costs in executive session.

ACTION: Amended to reorganize questions to ask about concomitant insulin use in #6 of the criteria. Modified criteria to allow use of basal insulin when in combination with a GLP-1 and specifically allow auto-PA for patients with claims for metformin use in the previous 40 days.

Motion to approve, 2nd, All in Favor

III. DUR ACTIVITIES

A. Quarterly Utilization Report – Mr. Citron presented the Quarterly Utilization Report
B. ProDUR Report – Mr. Holsapple presented the ProDUR Report
C. RetroDUR Report – Dr. Engen presented the RetroDUR Report
D. Oregon State Drug Reviews
    1. Updates on Testosterone Therapy
    2. Basal Insulin Update

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

IV. DUR OLD BUSINESS

A. Calcium/Vitamin D Prior Authorization Update
Dr. Sentena presented the proposal to:
- Add a vitamin D solution suitable for infants to the Practitioner-Managed Prescription Drug Plan (PMPDP)
- Evaluate comparative costs in executive session.

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

B. Hydroxyprogesterone Prior Authorization Update
Dr. Servid presented the proposal to:

- Update PA criteria to accommodate new generics for Makena®.

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

C. Benzodiazepine Prior Authorization Update
Dr. Servid presented the proposal to:

- Update PA criteria to include outpatient management of alcohol withdrawal syndrome.

ACTION: Amended to add prescribing specialists in mental health to questions #9 and #11.

Motion to approve, 2nd, all in favor

D. Cannabidiol Prior Authorization Update
Dr. Moretz presented the proposal to:

- Update PA criteria to include maximum dose limits.

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

V. PREFERRED DRUG LIST NEW BUSINESS

A. Tetracycline Class Update and New Drug Evaluation
Dr. Sentena presented the proposal to:

- Make no changes to the PMPDP based on clinical evidence.
- Evaluate comparative drug costs in executive session.

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

B. Hereditary Angioedema Agents Class Review
Dr. Servid presented the proposal to:

- Implement PA criteria to promote use for appropriate indications and ensure safe use.
- Make ecallantide non-preferred due to concerns with anaphylaxis.
- Evaluate comparative costs in executive session.

ACTION: amend proposed PA criteria to require laboratory documentation of diagnosis, add dosing table, and move question regarding preferred/nonpreferred drugs to later in PA after all clinical criteria are met.

Motion to approve, 2nd, all in favor

C. Endometriosis Class Review
Dr. Moretz presented the proposal to:

- Combine PA criteria for GnRH analogs and antagonists into one criteria entitled GnRH Modifiers and retire previous criteria.
- Revise step therapy for elagolix to remove requirement for trial of acetaminophen or a nonsteroidal anti-inflammatory agent.
- Add endometriosis diagnosis with step therapy for leuprolide, goserelin, and nafarelin.
- Reinforce warnings about bone mineral density (BMD) loss with use of GnRH modifiers.
- Evaluate comparative costs of GNRH analogs and antagonists in executive session

ACTION: Amended to limit approval to the FDA approved duration for GnRH analogues

Motion to approve, 2nd, all in favor

VI. DUR NEW BUSINESS

A. Mental Health Clinical Advisory Group
Ms. Parish provided some background on the work of the MHCAG and announced that the schizophrenia algorithm that was developed was published today.

Drs. Fussell and Cheng shared the process employed in the development of the algorithm, the hope that it will be a useful tool to the state. There was also discussion about the bi-polar algorithm that they are next developing.

B. Antipsychotics for Schizophrenia Drug Use Evaluation & Literature Scan
Drs. Moretz and Servid presented the proposal to:
   - Make no changes to the PMPDP for oral or parenteral antipsychotics based on clinical evidence.
   - Continue to explore opportunities for provider education and retrospective DUR initiatives.
   - Evaluate costs in executive session.

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

VII. EXECUTIVE SESSION

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

Members Present by Phone: Kelley Burnett, DO; Dave Pass, MD

Staff Present: Roger Citron, RPh; Sarah Servid, PharmD; David Engen, PharmD, CGP; Deanna Moretz, PharmD, BCPS; Kara Shirley, PharmD, BCACP, BCPS, BCPP; Richard Holsapple, RPh Dee Weston; Jennifer Torkelson; Brandon Wells; Jonnaliz Corbett; Trevor Douglass, DC, MPH

Staff Present by Phone: Kathy Sentena, PharmD

VIII. RECONVENE FOR PUBLIC RECOMMENDATIONS * After executive session

A. GLP-1 Receptor Agonists Literature Scan
Recommendation: Add exenatide vials (Bydureon) and liraglutide (Victoza 2 and 3 Pak) to the PDL. Allow auto PA of preferred therapies if patient has a history of metformin use (previous or current)
ACTION: Motion to approve items, 2nd, majority in favor with one opposed

B. Calcium/Vitamin D Prior Authorization Update
Recommendation: Make cholecalciferol (vitamin D3) (Baby Ddrops) preferred on the PMPDP
ACTION: Motion to approve items, 2nd, all in favor

C. Tetracycline Class Update and New Drug Evaluation
Recommendation: no changes to the PMPDP
ACTION: Motion to approve items, 2nd, all in favor

D. Hereditary Angioedema Agents Class Review
Recommendation: Make C1 esterase inhibitor (Berinert®) and C1 esterase inhibitor (Haegarda®) preferred on the PMPDP
ACTION: Motion to approve items, 2nd, all in favor

E. Endometriosis Class Review
Recommendation: no changes to the PMPDP
ACTION: Motion to approve items, 2nd, all in favor

F. Antipsychotics Literature Scan
Recommendation: no changes to the PMPDP
ACTION: Motion to approve items, 2nd, all in favor

IX. ADJOURN

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Pharmacy Utilization Summary Report: October 2017 - September 2018

Eligibility	Oct-17	Nov-17	Dec-17	Jan-18	Feb-18	Mar-18	Apr-18	May-18	Jun-18	Jul-18	Aug-18	Sep-18	Avg Monthly
Total Members (FFS & Encounter)	961,528	962,260	963,814	961,458	959,824	963,504	965,503	964,592	965,132	962,205	964,077	963,131	963,086
FFS Members	128,336	118,961	126,786	121,061	121,425	120,975	121,038	113,512	117,714	120,682	119,156	121,522	120,931
OHP Basic with Medicare	33,710	33,679	33,770	33,777	34,033	34,222	34,378	34,471	34,742	34,887	35,039	35,293	34,333
OHP Basic without Medicare	12,541	11,983	12,096	12,068	12,220	12,198	12,207	11,665	11,817	11,917	11,827	11,956	12,041
ACA	82,085	73,299	80,920	75,216	75,172	74,555	74,453	67,376	71,155	73,878	72,290	74,273	74,556
Encounter Members	833,192	843,299	837,028	840,397	838,399	842,529	844,465	851,080	847,418	841,523	844,921	841,609	842,155
OHP Basic with Medicare	41,080	41,162	41,174	41,156	41,089	41,117	41,143	41,324	41,337	41,300	41,375	41,334	41,216
OHP Basic without Medicare	63,025	63,731	63,827	63,767	63,431	63,435	63,126	63,424	63,149	62,869	62,744	62,264	63,233
ACA	729,087	738,406	732,027	735,474	733,879	737,977	740,196	746,332	742,932	737,354	740,802	738,011	737,706

Gross Cost Figures for Drugs	Oct-17	Nov-17	Dec-17	Jan-18	Feb-18	Mar-18	Apr-18	May-18	Jun-18	Jul-18	Aug-18	Sep-18	YTD Sum
Total Amount Paid (FFS & Encounter)	$73,640,970	$73,181,926	$70,009,882	$81,169,389	$71,565,092	$79,270,693	$76,218,175	$78,910,342	$74,457,274	$75,505,932	$79,626,563	$69,712,494	$903,268,731
Mental Health Carve-Out Drugs	$7,573,468	$7,267,459	$7,024,290	$7,925,947	$7,114,854	$7,700,187	$7,636,456	$7,949,914	$7,575,265	$7,682,157	$7,928,455	$7,134,568	$90,513,020
OHP Basic with Medicare	$282	$61	$36	$2,895	$73	$2,609	$1,634	$56	$39	$4,450	$6,085	$4,293	$22,512
OHP Basic without Medicare	$3,121,094	$3,033,932	$3,000,440	$3,288,120	$3,031,375	$3,241,144	$3,203,253	$3,345,172	$3,221,488	$3,199,073	$3,338,023	$2,946,168	$37,969,283
ACA	$4,394,267	$4,171,299	$3,965,588	$4,579,923	$4,029,579	$4,405,932	$4,376,067	$4,552,324	$4,301,913	$4,424,575	$4,522,013	$4,132,659	$51,856,139
FFS Physical Health Drugs	$2,845,998	$2,635,234	$2,706,510	$3,521,480	$2,970,054	$3,006,648	$2,905,073	$2,996,668	$2,743,400	$2,794,437	$3,070,282	$2,513,696	$34,709,481
OHP Basic with Medicare	$240,239	$235,632	$206,537	$261,260	$237,428	$251,590	$240,637	$274,446	$226,999	$228,072	$236,947	$213,275	$2,853,061
OHP Basic without Medicare	$956,368	$858,129	$889,590	$1,255,848	$950,195	$933,916	$932,800	$1,010,681	$855,897	$822,573	$962,045	$717,428	$11,145,470
ACA	$1,533,731	$1,404,305	$1,495,023	$1,869,024	$1,644,682	$1,681,910	$1,581,458	$1,572,854	$1,528,930	$1,611,551	$1,703,472	$1,461,142	$19,088,082
FFS Physician Administered Drugs	$1,355,545	$1,820,595	$1,368,347	$2,465,758	$2,349,999	$1,818,114	$1,864,731	$1,977,107	$2,206,949	$1,786,216	$1,948,972	$1,537,074	$22,499,407
OHP Basic with Medicare	$386,436	$545,082	$466,423	$557,887	$441,912	$495,801	$529,275	$563,490	$486,088	$406,670	$496,069	$448,464	$5,823,596
OHP Basic without Medicare	$328,156	$505,407	$269,877	$505,708	$884,203	$313,303	$124,541	$321,645	$576,999	$321,980	$442,123	$245,651	$4,839,594
ACA	$433,133	$519,143	$441,193	$1,034,804	$683,757	$667,565	$568,621	$672,669	$714,734	$627,603	$672,267	$533,402	$7,568,891
Encounter Physical Health Drugs	$50,081,317	$49,509,111	$48,085,698	$54,099,993	$48,009,867	$54,568,043	$51,499,803	$53,604,352	$50,448,511	$50,259,489	$53,129,122	$47,471,449	$610,766,754
OHP Basic with Medicare	$132,811	$126,742	$111,339	$135,217	$138,314	$154,992	$116,901	$132,319	$126,448	$190,479	$271,566	$228,476	$1,865,603
OHP Basic without Medicare	$13,402,343	$13,336,329	$12,472,544	$13,939,098	$12,377,156	$14,269,082	$13,406,638	$13,919,708	$13,291,709	$13,363,342	$14,013,084	$12,436,413	$160,227,445
ACA	$35,833,080	$35,340,966	$34,801,735	$39,258,078	$34,811,089	$39,407,985	$37,250,656	$38,835,729	$36,415,872	$36,088,951	$38,169,624	$34,139,107	$440,352,872
Encounter Physician Administered Drugs	$11,784,642	$11,949,526	$10,825,037	$13,156,210	$11,120,319	$12,177,700	$12,312,112	$12,382,301	$11,483,149	$12,983,634	$13,549,733	$11,055,706	$144,780,068
OHP Basic with Medicare	$208,069	$198,369	$201,379	$328,273	$256,849	$314,364	$276,044	$283,460	$255,766	$307,676	$277,389	$236,577	$3,144,215
OHP Basic without Medicare	$2,241,755	$2,628,999	$2,284,679	$3,128,320	$2,465,739	$2,542,908	$3,018,337	$2,893,496	$2,463,250	$3,130,519	$3,034,330	$2,656,681	$32,489,012
ACA	$9,022,807	$8,851,195	$8,168,588	$9,515,686	$8,274,902	$9,152,157	$8,732,010	$9,042,014	$8,631,593	$9,270,864	$10,071,648	$8,031,393	$106,764,858

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

Last Updated: April 17, 2019

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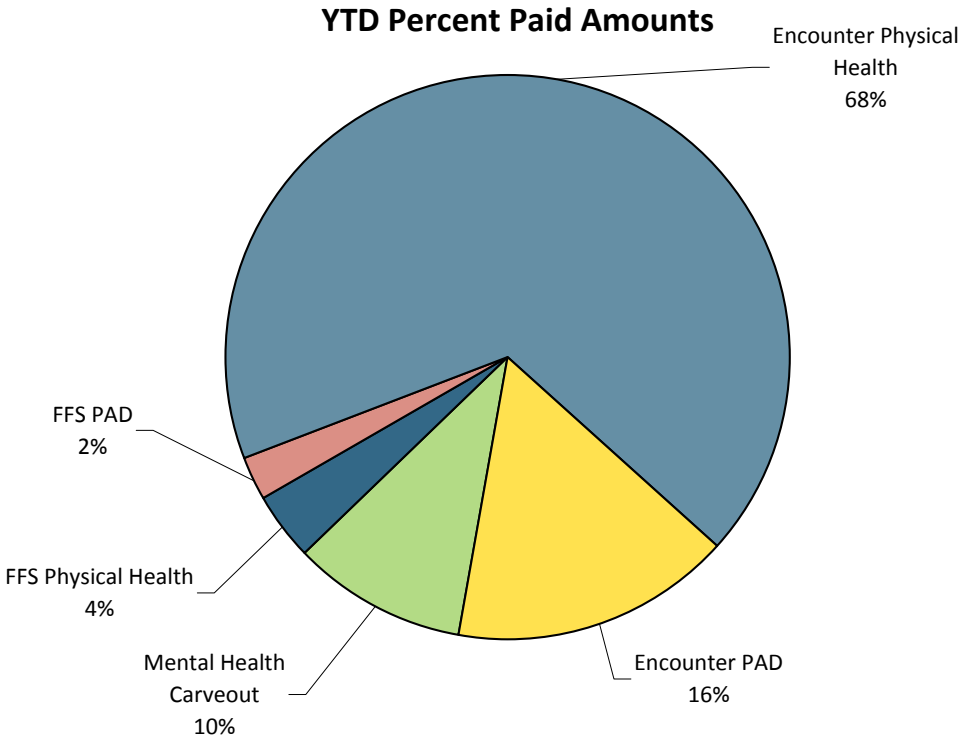
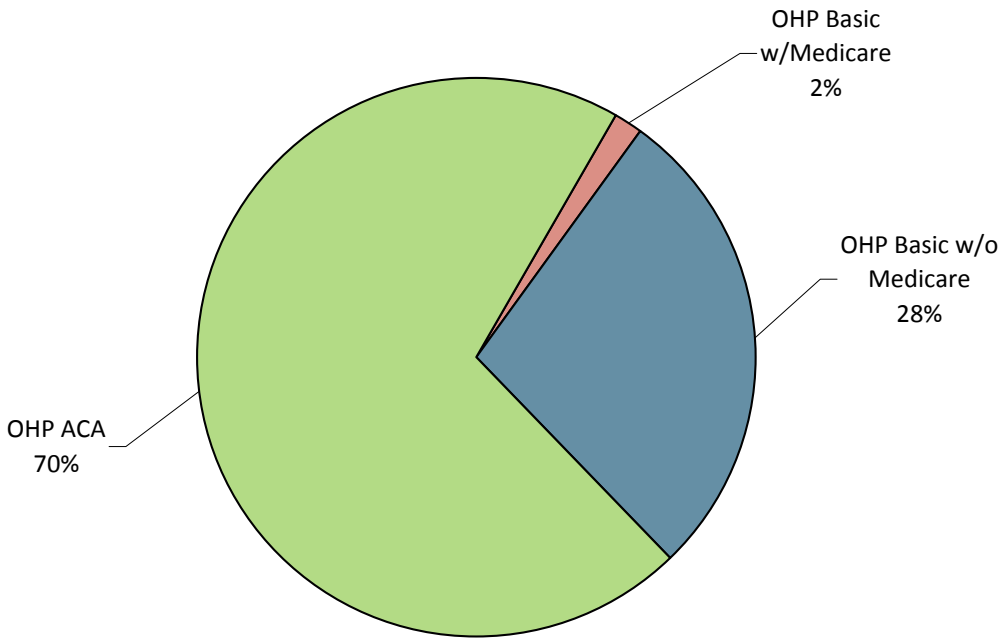
Pharmacy Utilization Summary Report: October 2017 - September 2018





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

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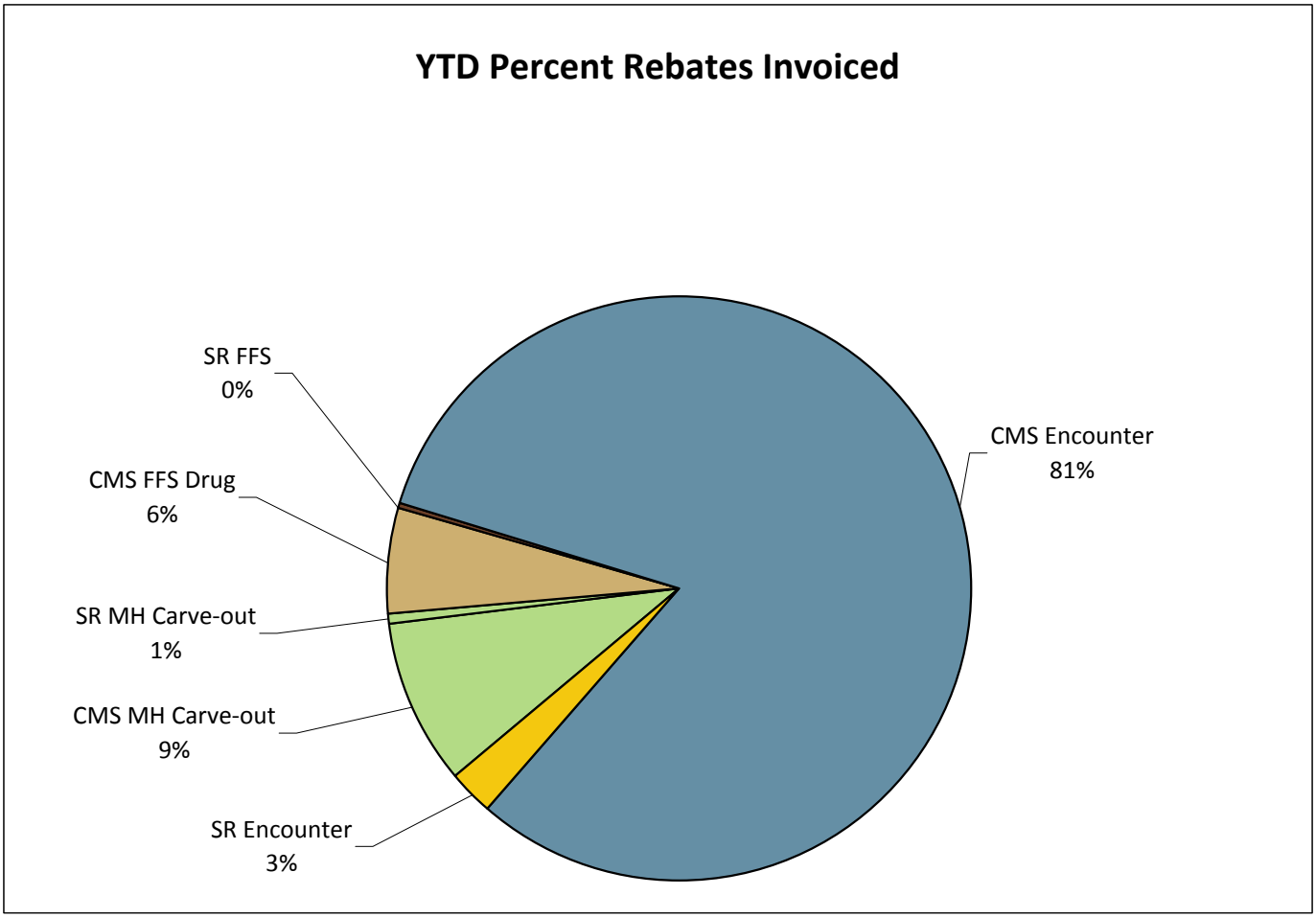
Pharmacy Utilization Summary Report: October 2017 - September 2018

Quarterly Rebates Invoiced	2017-Q4	2018-Q1	2018-Q2	2018-Q3	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$100,726,268	$109,343,177	$107,457,197	$103,499,304	$421,025,946
CMS MH Carve-out	$8,953,075	$9,690,640	$9,878,635	$9,861,372	$38,383,721
SR MH Carve-out	$654,794	$533,658	$559,564	$573,545	$2,321,560
CMS FFS Drug	$5,690,767	$6,887,248	$6,428,386	$6,170,653	$25,177,053
SR FFS	$185,410	$220,900	$216,589	$238,767	$861,667
CMS Encounter	$82,619,069	$89,188,504	$87,521,852	$84,018,857	$343,348,281
SR Encounter	$2,623,153	$2,822,227	$2,852,172	$2,636,111	$10,933,664

Quaterly Net Drug Costs	2017-Q4	2018-Q1	2018-Q2	2018-Q3	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$116,106,509	$122,661,996	$122,128,594	$121,345,685	$482,242,785
Mental Health Carve-Out Drugs	$12,257,349	$12,516,691	$12,723,437	$12,310,263	$49,807,739
FFS Phys Health + PAD	$6,856,053	$9,023,905	$8,048,954	$7,241,257	$31,170,169
Encounter Phys Health + PAD	$96,993,108	$101,121,401	$101,356,203	$101,794,165	$401,264,877



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

Last Updated: April 17, 2019

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Pharmacy Utilization Summary Report: October 2017 - September 2018

Gross PMPM Drug Costs (Rebates not Subtracted)	Oct-17	Nov-17	Dec-17	Jan-18	Feb-18	Mar-18	Apr-18	May-18	Jun-18	Jul-18	Aug-18	Sep-18	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$76.59	$76.05	$72.64	$84.42	$74.56	$82.27	$78.94	$81.81	$77.15	$78.47	$82.59	$72.38	$78.16
Mental Health Carve-Out Drugs	$7.88	$7.55	$7.29	$8.24	$7.41	$7.99	$7.91	$8.24	$7.85	$7.98	$8.22	$7.41	$7.83
FFS Physical Health Drugs	$22.18	$22.15	$21.35	$29.09	$24.46	$24.85	$24.00	$26.40	$23.31	$23.16	$25.77	$20.69	$23.95
FFS Physician Administered Drugs	$10.56	$15.30	$10.79	$20.37	$19.35	$15.03	$15.41	$17.42	$18.75	$14.80	$16.36	$12.65	$15.57
Encounter Physical Health Drugs	$60.11	$58.71	$57.45	$64.37	$57.26	$64.77	$60.99	$62.98	$59.53	$59.72	$62.88	$56.41	$60.43
Encounter Physician Administered Drugs	$14.14	$14.17	$12.93	$15.65	$13.26	$14.45	$14.58	$14.55	$13.55	$15.43	$16.04	$13.14	$14.33

Claim Counts	Oct-17	Nov-17	Dec-17	Jan-18	Feb-18	Mar-18	Apr-18	May-18	Jun-18	Jul-18	Aug-18	Sep-18	Avg Monthly
Total Claim Count (FFS & Encounter)	1,051,383	1,020,527	1,005,980	1,117,999	972,356	1,077,613	1,050,805	1,089,003	1,017,475	1,017,270	1,046,551	967,350	1,036,193
Mental Health Carve-Out Drugs	153,641	149,558	145,490	159,755	141,766	155,512	153,724	159,271	149,540	152,645	157,357	144,469	151,894
FFS Physical Health Drugs	60,714	56,901	56,437	66,824	59,132	61,715	59,103	59,948	56,109	55,290	57,564	52,334	58,506
FFS Physician Administered Drugs	17,988	16,914	16,470	26,329	20,918	21,517	20,511	21,013	19,094	19,705	18,013	14,495	19,414
Encounter Physical Health Drugs	701,816	682,551	675,698	738,750	643,733	721,152	700,607	727,446	680,682	674,440	697,452	648,527	691,071
Encounter Physician Administered Drugs	117,224	114,603	111,885	126,341	106,807	117,717	116,860	121,325	112,050	115,190	116,165	107,525	115,308

Gross Amount Paid per Claim (Rebates not Subtracted)	Oct-17	Nov-17	Dec-17	Jan-18	Feb-18	Mar-18	Apr-18	May-18	Jun-18	Jul-18	Aug-18	Sep-18	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$70.04	$71.71	$69.59	$72.60	$73.60	$73.56	$72.53	$72.46	$73.18	$74.22	$76.08	$72.07	$72.64
Mental Health Carve-Out Drugs	$49.29	$48.59	$48.28	$49.61	$50.19	$49.52	$49.68	$49.91	$50.66	$50.33	$50.39	$49.38	$49.65
FFS Physical Health Drugs	$46.88	$46.31	$47.96	$52.70	$50.23	$48.72	$49.15	$49.99	$48.89	$50.54	$53.34	$48.03	$49.39
FFS Physician Administered Drugs	$75.36	$107.64	$83.08	$93.65	$112.34	$84.50	$90.91	$94.09	$115.58	$90.65	$108.20	$106.04	$96.84
Encounter Physical Health Drugs	$71.36	$72.54	$71.16	$73.23	$74.58	$75.67	$73.51	$73.69	$74.11	$74.52	$76.18	$73.20	$73.65
Encounter Physician Administered Drugs	$100.53	$104.27	$96.75	$104.13	$104.12	$103.45	$105.36	$102.06	$102.48	$112.71	$116.64	$102.82	$104.61

Gross Amount Paid per Claim - Multi Source Drugs (Rebates not Subtracted)	Oct-17	Nov-17	Dec-17	Jan-18	Feb-18	Mar-18	Apr-18	May-18	Jun-18	Jul-18	Aug-18	Sep-18	Avg Monthly
Multi-Source Drugs: Average Paid / Claim (FFS & Encounter)	$30.93	$31.36	$30.75	$30.53	$29.91	$29.96	$29.38	$29.17	$28.94	$28.81	$29.18	$28.34	$29.77
Mental Health Carve-Out Drugs	$24.66	$23.78	$23.45	$23.77	$23.88	$23.06	$22.62	$22.76	$22.75	$22.86	$22.74	$21.24	$23.13
FFS Physical Health Drugs	$25.27	$24.33	$25.42	$25.78	$26.05	$24.66	$24.24	$24.06	$24.29	$24.16	$26.45	$24.61	$24.94
Encounter Physical Health Drugs	$32.85	$33.67	$32.83	$32.47	$31.65	$31.95	$31.35	$31.04	$30.73	$30.58	$30.90	$30.28	$31.69

Gross Amount Paid per Claim - Single Source Drugs (Rebates not Subtracted)	Oct-17	Nov-17	Dec-17	Jan-18	Feb-18	Mar-18	Apr-18	May-18	Jun-18	Jul-18	Aug-18	Sep-18	Avg Monthly
Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$583.76	$638.78	$658.14	$684.31	$727.99	$756.17	$742.36	$759.69	$760.39	$781.17	$787.95	$731.33	$717.67
Mental Health Carve-Out Drugs	$928.66	$933.46	$964.37	$981.02	$1,011.84	$1,003.27	$1,021.42	$1,010.48	$1,034.06	$1,022.65	$1,012.82	$1,021.98	$995.50
FFS Physical Health Drugs	$344.52	$377.01	$386.16	$456.99	$422.09	$440.34	$448.50	$469.58	$441.69	$487.61	$485.01	$421.51	$431.75
Encounter Physical Health Drugs	$574.53	$632.60	$652.94	$677.21	$728.82	$758.27	$738.95	$757.67	$758.55	$778.93	$788.79	$725.73	$714.42

Multi-Source Drug Use Percentage	Oct-17	Nov-17	Dec-17	Jan-18	Feb-18	Mar-18	Apr-18	May-18	Jun-18	Jul-18	Aug-18	Sep-18	Avg Monthly
Multi-Source Drug Use Percentage	93.6%	94.2%	94.4%	94.3%	94.4%	94.5%	94.6%	94.7%	94.6%	94.7%	94.6%	94.4%	94.4%
Mental Health Carve-Out Drugs	97.3%	97.3%	97.4%	97.3%	97.3%	97.3%	97.3%	97.3%	97.2%	97.3%	97.2%	97.2%	97.3%
FFS Physical Health Drugs	93.2%	93.8%	93.8%	93.8%	93.9%	94.2%	94.1%	94.2%	94.1%	94.3%	94.1%	94.1%	94.0%
Encounter Physical Health Drugs	92.9%	93.5%	93.8%	93.7%	93.8%	94.0%	94.0%	94.1%	94.0%	94.1%	94.0%	93.8%	93.8%

Preferred Drug Use Percentage	Oct-17	Nov-17	Dec-17	Jan-18	Feb-18	Mar-18	Apr-18	May-18	Jun-18	Jul-18	Aug-18	Sep-18	Avg Monthly
Preferred Drug Use Percentage	86.91%	86.73%	86.68%	87.09%	86.96%	86.86%	86.63%	86.73%	86.57%	86.40%	86.20%	86.07%	86.7%
Mental Health Carve-Out Drugs	74.66%	74.47%	74.52%	74.51%	74.36%	74.45%	74.17%	74.23%	73.93%	74.05%	73.87%	73.89%	74.3%
FFS Physical Health Drugs	95.38%	95.54%	95.48%	95.75%	95.62%	95.59%	95.54%	95.46%	95.76%	95.62%	95.76%	95.84%	95.6%
Encounter Physical Health Drugs	88.88%	88.68%	88.57%	89.04%	88.95%	88.79%	88.62%	88.75%	88.58%	88.44%	88.19%	88.02%	88.6%

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

Last Updated: April 17, 2019

Drug Use Research & Management Program
DHS - Health Systems Division
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Top 40 Drugs by Gross Amount Paid (FFS Only) - First Quarter 2019

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	LATUDA	Antipsychotics, 2nd Gen	$5,543,231	15.2%	4,708	$1,177	Y
2	INVEGA SUSTENNA	Antipsychotics, Parenteral	$2,562,730	7.0%	1,346	$1,904	Y
3	ABILIFY MAINTENA	Antipsychotics, Parenteral	$1,305,482	3.6%	687	$1,900	Y
4	REXULTI	Antipsychotics, 2nd Gen	$1,217,965	3.3%	1,144	$1,065	V
5	VRAYLAR	Antipsychotics, 2nd Gen	$895,149	2.5%	804	$1,113	Y
6	INVEGA TRINZA	Antipsychotics, Parenteral	$663,063	1.8%	113	$5,868	Y
7	PALIPERIDONE ER	Antipsychotics, 2nd Gen	$539,184	1.5%	1,694	$318	V
8	SAPHRIS	Antipsychotics, 2nd Gen	$538,411	1.5%	817	$659	Y
9	Epoetin Alfa, 100 Units Esrd	Physican Administered Drug	$522,600	1.4%	1,817	$288	
10	FLUOXETINE HCL	Antidepressants	$496,948	1.4%	32,486	$15	Y
11	TRINTELLIX	Antidepressants	$468,246	1.3%	1,227	$382	V
12	DULOXETINE HCL	Antidepressants	$451,631	1.2%	29,870	$15	V
13	BUPROPION XL	Antidepressants	$444,310	1.2%	23,566	$19	V
14	SERTRALINE HCL	Antidepressants	$428,358	1.2%	43,069	$10	Y
15	ATOMOXETINE HCL*	ADHD Drugs	$423,400	1.2%	5,419	$78	Y
16	VIIBRYD	Antidepressants	$401,738	1.1%	1,436	$280	V
17	TRAZODONE HCL	Antidepressants	$395,879	1.1%	38,801	$10	
18	ENBREL SURECLICK*	Biologics for Autoimmune Conditions	$383,848	1.1%	100	$3,838	Y
19	RISPERDAL CONSTA*	Antipsychotics, Parenteral	$378,720	1.0%	419	$904	Y
20	Inj, Nusinersen, 0.1mg	Physican Administered Drug	$331,894	0.9%	2	$165,947	
21	ARISTADA	Antipsychotics, Parenteral	$320,565	0.9%	161	$1,991	Y
22	LAMOTRIGINE ER	Antiepileptics (oral & rectal)	$271,260	0.7%	1,901	$143	V
23	VENLAFAXINE HCL ER	Antidepressants	$269,859	0.7%	1,806	$149	V
24	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	$264,262	0.7%	17,174	$15	
25	Factor Viii Recombinant Nos	Physican Administered Drug	$258,522	0.7%	19	$13,606	
26	ESCITALOPRAM OXALATE	Antidepressants	$246,082	0.7%	24,951	$10	Y
27	LAMOTRIGINE	Antiepileptics (oral & rectal)	$232,743	0.6%	22,643	$10	Y
28	ARIPIPRAZOLE	Antipsychotics, 2nd Gen	$229,494	0.6%	14,125	$16	V
29	CONCERTA*	ADHD Drugs	$221,549	0.6%	880	$252	N
30	AMITRIPTYLINE HCL	Antidepressants	$209,664	0.6%	14,846	$14	Y
31	CITALOPRAM HBR	Antidepressants	$193,376	0.5%	21,698	$9	Y
32	HUMIRA PEN*	Biologics for Autoimmune Conditions	$188,541	0.5%	74	$2,548	Y
33	VENLAFAXINE HCL ER	Antidepressants	$184,164	0.5%	14,709	$13	Y
34	QUETIAPINE FUMARATE*	Antipsychotics, 2nd Gen	$175,703	0.5%	15,471	$11	Y
35	EPCLUSA*	Hepatitis C, Direct-Acting Antivirals	$160,883	0.4%	11	$14,626	Y
36	LANTUS SOLOSTAR*	Diabetes, Insulins	$158,345	0.4%	500	$317	Y
37	FETZIMA	Antidepressants	$156,239	0.4%	383	$408	V
38	Inj Pembrolizumab	Physican Administered Drug	$154,724	0.4%	59	$2,622	
39	CHLORPROMAZINE HCL	Antipsychotics, 1st Gen	$149,997	0.4%	579	$259	V
40	BUPROPION HCL SR	Antidepressants	$140,843	0.4%	10,371	$14	Y
		Top 40 Aggregate:	**$22,579,603**		**351,886**	**$5,571**	
		All FFS Drugs Totals:	**$36,523,485**		**668,219**	**$513**	

*** Drug requires Prior Authorization**

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

Last updated: April 17, 2019

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Top 40 Physical Health Drugs by Gross Amount Paid (FFS Only) - First Quarter 2019

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	Epoetin Alfa, 100 Units Esrd	Physican Administered Drug	$522,600	4.0%	1,817	$288	
2	ENBREL SURECLICK*	Biologics for Autoimmune Conditions	$383,848	3.0%	100	$3,838	Y
3	Inj, Nusinersen, 0.1mg	Physican Administered Drug	$331,894	2.6%	2	$165,947	
4	Factor Viii Recombinant Nos	Physican Administered Drug	$258,522	2.0%	19	$13,606	
5	CONCERTA*	ADHD Drugs	$221,549	1.7%	880	$252	N
6	HUMIRA PEN*	Biologics for Autoimmune Conditions	$188,541	1.5%	74	$2,548	Y
7	EPCLUSA*	Hepatitis C, Direct-Acting Antivirals	$160,883	1.2%	11	$14,626	Y
8	LANTUS SOLOSTAR*	Diabetes, Insulins	$158,345	1.2%	500	$317	Y
9	Inj Pembrolizumab	Physican Administered Drug	$154,724	1.2%	59	$2,622	
10	NOVOLOG FLEXPEN	Diabetes, Insulins	$133,130	1.0%	281	$474	Y
11	Injection, Nivolumab	Physican Administered Drug	$132,977	1.0%	52	$2,557	
12	Drugs Unclassified Injection	Physican Administered Drug	$128,837	1.0%	4,144	$31	
13	HYDROXYPROGESTERONE CAPROAT	Progestational Agents	$116,050	0.9%	62	$1,872	N
14	Injection, Pegfilgrastim 6mg	Physican Administered Drug	$113,952	0.9%	40	$2,849	
15	Etonogestrel Implant System	Physican Administered Drug	$113,021	0.9%	192	$589	
16	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$112,909	0.9%	10	$11,291	Y
17	Injection, Doxercalciferol	Physican Administered Drug	$107,129	0.8%	257	$417	
18	Infliximab Not Biosimil 10mg	Physican Administered Drug	$107,059	0.8%	70	$1,529	
19	LANTUS	Diabetes, Insulins	$105,873	0.8%	316	$335	Y
20	Factor Viii Pegylated Recomb	Physican Administered Drug	$100,875	0.8%	5	$20,175	
21	HUMIRA*	Biologics for Autoimmune Conditions	$100,119	0.8%	22	$4,551	Y
22	SYNAGIS*	STC 33 - Antivirals	$99,993	0.8%	50	$2,000	
23	GENVOYA	HIV	$99,215	0.8%	39	$2,544	Y
24	ADVATE	Antihemophilia Factors	$97,637	0.8%	6	$16,273	
25	VYVANSE*	ADHD Drugs	$97,441	0.8%	671	$145	Y
26	PROAIR HFA	Beta-Agonists, Inhaled Short-Acting	$96,875	0.7%	1,467	$66	Y
27	Inj., Emicizumab-Kxwh 0.5 Mg	Physican Administered Drug	$96,065	0.7%	3	$32,022	
28	NUVARING	STC 63 - Oral Contraceptives	$95,984	0.7%	370	$259	
29	BIKTARVY	HIV	$95,143	0.7%	38	$2,504	Y
30	Mirena, 52 Mg	Physican Administered Drug	$93,893	0.7%	155	$606	
31	FLOVENT HFA	Corticosteroids, Inhaled	$91,824	0.7%	579	$159	Y
32	Aflibercept Injection	Physican Administered Drug	$89,779	0.7%	201	$447	
33	ORKAMBI*	Cystic Fibrosis	$88,568	0.7%	17	$5,210	N
34	TRUVADA	HIV	$85,755	0.7%	78	$1,099	Y
35	HUMALOG	Diabetes, Insulins	$84,777	0.7%	232	$365	Y
36	SYMBICORT	Corticosteroids/LABA Combination, Inhaled	$84,762	0.7%	319	$266	Y
37	Factor Viii Recomb Novoeight	Physican Administered Drug	$81,338	0.6%	5	$16,268	
38	CHANTIX*	Tobacco Smoking Cessation	$81,217	0.6%	221	$367	Y
39	VIMPAT	Antiepileptics (oral & rectal)	$79,199	0.6%	197	$402	Y
40	ENBREL*	Biologics for Autoimmune Conditions	$78,930	0.6%	14	$5,638	Y
		Top 40 Aggregate:	**$5,471,231**		**13,575**	**$8,434**	
		All FFS Drugs Totals:	**$12,948,125**		**200,707**	**$524**	

*** Drug requires Prior Authorization**

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

Last updated: April 17, 2019

ProDUR Report for January through March 2019
High Level Summary by DUR Alert

DUR Alert	Example	Disposition	# Alerts	# Overrides	# Cancellations	# Non-Response	% of all DUR Alerts	% Overridden
DA (Drug/Allergy Interaction)	Amoxicillin billed and Penicillin allergy on patient profile	Set alert/Pay claim	7	3	0	4	0.01%	42.9%
DC (Drug/Inferred Disease Interaction)	Quetiapine billed and condition on file for Congenital Long QT Sundrome	Set alert/Pay claim	1,423	294	0	1,127	1.20%	20.7%
DD (Drug/Drug Interaction)	Linezolid being billed and patient is on an SNRI	Set alert/Pay claim	191	50	0	141	0.13%	26.2%
ER (Early Refill)	Previously filled 30 day supply and trying to refill after 20 days (80% = 24 days)	Set alert/Deny claim	78,125	13,776	95	63,944	68.50%	17.6%
ID (Ingredient Duplication)	Oxycodone IR 15mg billed and patient had Oxycodone 40mg ER filled in past month	Set alert/Pay claim	24,228	6,004	11	18,173	21.20%	24.8%
LD (Low Dose)	Divalproex 500mg ER billed for 250mg daily (#15 tabs for 30 day supply)	Set alert/Pay claim	719	126	0	591	0.60%	17.5%
LR (Late Refill/Underutilization)	Previously filled for 30 days supply and refill being billed 40 days later.	Set alert/Pay claim	3	2	0	1	0.01%	66.7%
MC (Drug/Disease Interaction)	Bupropion being billed and patient has a seizure disorder	Set alert/Pay claim	917	230	1	686	0.77%	25.1%
MX (Maximum Duration of Therapy)		Set alert/Pay claim	657	166	0	490	0.53%	25.3%
PG (Pregnancy/Drug Interaction)	Accutane billed and client has recent diagnosis history of pregnancy	Set alert/Deny claim	54	29	0	25	0.02%	53.7%
TD (Therapeutic Duplication)	Diazepam being billed and patient recently filled an Alprazolam claim.	Set alert/Pay claim	7,662	2,007	1	5,649	6.70%	26.2%
		Totals	**113,986**	**22,687**	**108**	**90,831**	**99.67%**	**19.9%**

ProDUR Report for January through March 2019

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)	1,465	235	1,230	11,744	12.5%	16.0%
ER	Lorazepam	471	107	364	14,557	3.2%	22.7%
ER	Alprazolam	347	59	288	9,278	3.7%	17.0%
ER	Diazepam	202	48	154	5,094	4.0%	23.8%
ER	Buspirone (Buspar)	2,275	361	1,914	27,171	8.4%	15.9%
ER	Lamictal (Lamotrigine)	4,218	734	3,483	34,832	12.1%	17.4%
ER	Seroquel (Quetiapine)	3,623	717	2,906	24,977	14.5%	19.8%
ER	Risperdal (Risperidone)	1,896	391	1,505	13,621	13.9%	20.6%
ER	Abilify (Aripiprazole)	2,687	472	2,215	20,990	12.8%	17.6%
ER	Wellbutrin (Bupropion)	4,462	718	3,744	49,124	9.1%	16.1%
ER	Hydrocodone/APAP	28	12	16	2,584	1.1%	42.9%
ER	Oxycodone	73	27	46	1,920	3.8%	37.0%
ER	Oxycodone/APAP	10	1	9	706	1.4%	10.0%
ER	Tramadol	15	8	7	676	2.2%	53.3%
ER	Zoloft (Sertraline)	5,611	951	4,660	54,787	10.2%	16.9%
ER	Prozac (Fluoxetine)	3,948	627	3,321	43,560	9.1%	15.9%
ER	Lexapro (Escitalopram)	3,121	488	2,632	32,888	9.5%	15.6%
ER	Celexa (Citalopram)	2,239	316	1,923	26,555	8.4%	14.1%
ER	Trazodone	5,501	868	4,632	49,374	11.1%	15.8%

ProDUR Report for January through March 2019

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-14 LTC Leave of Absence	CC-Other
ER	January	3,299	87	236	953	2	1,917	0	104
ER	February	3,576	102	237	1,025	4	2,100	1	107
ER	March	3,287	129	222	828	2	2,001	0	105
	Total =	**10,162**	**318**	**695**	**2,806**	**8**	**6,018**	**1**	**316**
	Percentage of total overrides =		**3.1%**	**6.8%**	**27.6%**	**0.1%**	**59.2%**	**0.0%**	**3.1%**

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Retro-DUR Intervention History by Quarter FFY 2018 - 2019

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Change Form	Fluoxetine Tabs to Caps	Unique Prescribers Identified	637			
		Unique Patients Identified	891			
		Prescriptions Changed to Recommended Within 6 Months of Intervention	308			
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$24,269			
	Lamotrigine ER to IR	Unique Prescribers Identified	363			
		Unique Patients Identified	652			
		Prescriptions Changed to Recommended Within 6 Months of Intervention	130			
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$60,491			

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Retro-DUR Intervention History by Quarter FFY 2018 - 2019

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Cost Savings	Dose Optimization	Total Claims Identified	88	101	39	
		Total Faxes Successfully Sent	35	48	11	
		Prescriptions Changed to Recommended Dose Within 3 Months of Fax Sent	29	28	3	
		Prescriptions Changed to Alternative Dose Within 3 Months of Fax Sent	6	22		
		Prescriptions Unchanged after 3 Months of Fax Sent	50	19		
		Safety Monitoring Profiles Identified	3	2		
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Faxes Sent	$43,734	$27,372	$1,676	

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Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Profile Review	Children under age 12 antipsychotic	RetroDUR_Profiles Reviewed	46	77		
	Children under age 18 on 3 or more psychotropics	RetroDUR_Profiles Reviewed	9	5		
	Children under age 18 on any psychotropic	RetroDUR_Profiles Reviewed	85	110		
	Children under age 6 on any psychotropic	RetroDUR_Profiles Reviewed	5	7		
	Dose Consolidation Safety Monitoring	RetroDUR_Profiles Reviewed		10		
	High Risk Patients - Polypharmacy	RetroDUR_Profiles Reviewed	19	12	11	
		RetroDUR_Letters Sent To Providers	2	2	3	
		Provider Responses	0	0	0	
		Provider Agreed / Found Info Useful	0	0	0	
	Lock-In	RetroDUR_Profiles Reviewed	52	5	9	
		RetroDUR_Letters Sent To Providers	3			
		Provider Responses	0			
		Provider Agreed / Found Info Useful	0			
		Locked In	3	0	0	
	Polypharmacy	RetroDUR_Profiles Reviewed	16	18	16	
		RetroDUR_Letters Sent To Providers	3	4	3	
		Provider Responses	0	0	0	
		Provider Agreed / Found Info Useful	0	0	0	

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2017-18 Year in Review: Important Safety Updates

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The United States Food and Drug Administration (FDA) issues drug alerts and safety recommendations to inform patients and health care practitioners of urgent precautions which improve patient care. Drugs are often approved by the FDA after evaluating safety and efficacy in short-term trials. Once these medications are marketed, post-surveillance monitoring continues to further evaluate safety. As new drugs are used in the general population, important safety signals become apparent. The purpose of this newsletter is to provide an update on relevant safety alerts published from 2017 through 2018.

Sodium-glucose-cotransporter-2 (SGLT2) Inhibitors

Fournier's Gangrene: In 2018, the FDA warned of rare but serious cases of genital and perigenital infections with the use of sodium-glucose cotransporter-2 (SGTL2) inhibitors. In the last five years, 12 cases of Fournier's gangrene (also known as necrotizing fasciitis) were reported in patients taking a SGTL2 inhibitor.[1] This effect has been reported with several drugs within this class, and is considered a class-wide effect resulting in labeling changes for all SGLT2 inhibitors. Fournier's gangrene severity should not be underestimated as mortality rates are high, ranging from 20% to 40%.[2] Potential risk factors for Fournier's gangrene are thought to be uncontrolled diabetes, obesity, smoking, urinary catherization, operative procedures, and recurrent fungal infections.[3]

Risk of amputation: In 2017, the FDA found an increased risk of leg and foot amputations with canagliflozin.[4] Results of the CANVAS trial showed leg and foot amputations occurred approximately twice as often in patients treated with canagliflozin compared to patients treated with placebo.[5] The risk of amputation was 5.9 out of every 1000 patients taking canagliflozin and 2.8 out of every 1000 patients treated with placebo per year, with a number needed to harm (NNH) of 323.[5] During the CANVAS-R 3-year follow up study, the amputation risk was found to be even higher, equivalent to 7.5 out of every 1,000 patients treated with canagliflozin and 4.2 out of every 1,000 patients treated with placebo with a NNH of 270 and a hazard ratio (HR) of 1.97 (95% CI, 1.41-2.75).[5] While only canagliflozin has a black-boxed warning for this risk, other SGTL2 inhibitors are being monitored to determine if this is a class effect.[6]

The drivers for amputation in patients with diabetes mellitus are complex and multi-factorial. A nationwide register based cohort study determined lower limb amputation to be a class wide effect, showing a hazard ratio of 2.32 for number of events per 1000 patient years with SGLT2 inhibitors compared to glucagon-like peptide-1 (GLP-1) receptor agonists.[7] In contrast, a large outcomes trial titled DECLARE-TIMI 58 evaluating the cardiovascular outcomes of dapagliflozin showed a non-significant risk of amputation.[8] Similarly, the EMPA-REG OUTCOME trial showed risk of lower limb amputation was similar between empagliflozin and placebo.[9] Determining whether drugs within a class exhibit similar or different therapeutic and safety profiles can be challenging in the absence of large randomized controlled trials (RCTs) with head-to-head comparisons.

Fluoroquinolone Safety

In July 2018, the FDA issued a warning about the possibility of life-threatening hypoglycemia and adverse psychiatric effects associated with fluoroquinolone antibiotics resulting in changes to prescribing information and patient medication guides. These findings were derived from post-marketing adverse event data including 56 reports in the FDA Adverse Event Reporting System (FAERS) from October 1987 through April 2017, and 11 additional cases in reported in the medical literature. The newest fluoroquinolone, delafloxacin, was not included in the FDA's review, but similar warnings are anticipated to be applied to this medication in the future.[10] More recently in December of 2018, another warning was added for increased occurrence of aortic aneurysm or dissection, leading to bleeding or death. This warning originated from case reports and four published observational studies.[11]

Risk of Hypoglycemia: Three of the fluoroquinolones (levofloxacin, ciprofloxacin, and ofloxacin) have a labeled warning about the risk of hypoglycemia when co-administered with sulfonylurea agents. Moxifloxacin also has a warning about possible dysglycemia in elderly patients receiving insulin or an oral hypoglycemic agent.[10] These warnings were strengthened to include risk of hypoglycemia leading to coma in July 2018 for the entire fluoroquinolone class; however, it is unclear if dysglycemia is a class effect, or specific to certain fluoroquinolones.

There are several proposed mechanisms for hypoglycemia due to exposure to fluoroquinolones. These hypotheses include pancreatic beta cell calcium release, blockade of ATP-sensitive potassium channels, magnesium deficiency leading to insulin resistance, or blockade of a gene that enhances insulin secretion.[12-15] The evidence related to dysglycemia has primarily been published in observational case reports and retrospective studies in patients with and without anti-diabetic agents or a diagnosis of diabetes. A retrospective cohort found an increased risk of dysglycemia with gatifloxacin and levofloxacin, but not ciprofloxacin, as shown in Table 1.[16]

Table 1: Risk of Dysglycemia with Fluoroquinolones[16]

Antibiotic	Hypoglycemia OR (95% CI)	Hyperglycemia OR (95% CI)
Patients with diabetes		
Levofloxacin	2.1 (1.4-3.3)*	1.8 (1.2-2.7)*
Ciprofloxacin	1.1 (0.6-2.0)	1.0 (0.6-1.8)
Patients without diabetes		
Levofloxacin	1.6 (0.4-6.6)	0.7 (0.3-1.7)
Ciprofloxacin	0.7 (0.1-6.9)	0.9 (0.3-2.6)
Key: * Statistically significant (P<0.05) Abbreviations: CI – confidence interval; OR – odds ratio		

A large cohort study (n=78,433) conducted in diabetic patients based in Taiwan concluded fluoroquinolones were associated with a higher, statistically significant risk of hypoglycemia compared with macrolides or cephalosporins (Table 2).[17]

Table 2: Hypoglycemia Associated with Selected Antibiotics[17]

Antibiotics	Incidence (%) per 1000 persons	Time to event, days mean ± SD	Adjusted OR (95% CI)
Macrolides (reference group)	1.62	6.32 +6.81	1.00
Moxifloxacin	9.95	7.02 + 9.51	2.13 (1.44-3.14)*
Levofloxacin	9.26	7.12 +8.48	1.79 (1.33-2.42)*
Ciprofloxacin	7.88	9.16 + 9.40	1.46 (1.07-2.0)*

Key: * Statistically significant (P<0.05)
Abbreviations: CI – confidence interval; OR – odds ratio; SD – standard deviation

In an analysis of the incidence of hypoglycemic coma submitted to the FDA, there were 67 identified case reports, mainly in older patients with renal insufficiency and concomitant use of anti-glycemic agents. Patients were treated with levofloxacin (n=44), ciprofloxacin (n=12), moxifloxacin (n=9), and ofloxacin (n=2).[10] Of the 67 total patients, 47 had diabetes (70%), with 41 (62%) reportedly taking at least one oral hypoglycemic drug and 35 (52%) taking a sulfonylurea specifically.[10] Twenty patients did not have a diabetes diagnosis (30%), and some patients were only being treated for uncomplicated infections. A total of 13 deaths occurred (19%), and 14 patients had disability or neurological injury (21%).[10] Although evidence is insufficient to determine which fluoroquinolone has the highest incidence of dysglycemia, there should be awareness surrounding the risk of hypoglycemic coma with fluoroquinolones.

Psychiatric Adverse Effects: The FDA recently updated the warnings and precautions section of the fluoroquinolone drug label concerning mental health side effects: disturbances in attention, disorientation, agitation, nervousness, memory impairment, and delirium.[10] The mechanism behind fluoroquinolone-associated delirium or psychosis is unknown, but is hypothesized to involve n-methyl-d-aspartate (NMDA) agonistic activity, and gamma-aminobutyric acid A (GABA) antagonism.[18-20] A retrospective, single center study conducted at a Veteran Affairs hospital between 2005 and 2014 found a 3.7% incidence of intravenous or oral fluoroquinolone-associated delirium/psychosis in the inpatient veteran population. This finding is higher than the current estimate of <1% from post marketing surveillance reported by the manufacturer.[21] Interestingly, all patients experienced hyperactive delirium, and there were no differences noted between the type of pre-existing psychiatric condition and manifestation of delirium/psychosis.[22] A review of 206 articles for fluoroquinolone-associated neurological and psychiatric adverse reactions found ciprofloxacin to be associated with the highest number of neurological and psychiatric adverse events compared to other fluoroquinolones.[23] Investigators concluded the psychiatric adverse effects are dose-dependent and in majority of cases, activated without presence of predisposing conditions. They noted that although the events were serious, they resolved upon discontinuation of the medication.[23]

Risk of Aortic Aneurysm: The use of fluoroquinolones has been associated with rupture or dissection of aortic aneurysms based on numerous epidemiological studies and case reports.[11] Many patients in these studies were found to have risk factors for aortic aneurysm which include peripheral atherosclerotic vascular diseases, hypertension, genetic blood vessel disorders and old age, making the event more likely.[24] Based on severity of the data findings, the FDA advises prescribing of fluoroquinolones to patients with or at risk for an aortic aneurysm only when no other treatment options are available. A summary of the evidence is highlighted in Table 3.

Table 3: Risk of aortic aneurysm or dissection[25-28]

Study type	Results (95% CI)	Time of Fluoroquinolone Use	Patient Age (yrs.)
Epidemiological[26]	RR 2.28 (1.67-3.13)*	Current or use in the prior year	≥70
Retrospective cohort[28]	HR 1.66 (1.2-2.46)*	First 60 days	≥50
	HR 0.67 (0.4-1.11)	Day 61-120	
Retrospective cohort[25]	HR 2.24 (2.02-2.49)	30-day risk window	≥65
Self-controlled analyses[27]	OR 2.41 (1.14-6.46)*	60 days	Mean of 71
	OR 2.41 (1.25-4.65)*	3-14 days of exposure	
	OR 2.83 (1.06-7.57)*	>14 days of exposure	

Key: * Statistically significant (P<0.05)
Abbreviations: CI – confidence interval; HR – hazard ratio; OR – odds ratio; RR – rate ratio

Other Updates and Ongoing Safety Investigations:

Clarithromycin

The FDA communicated an update this year regarding a previous safety issue issued in 2015 associated with prescribing clarithromycin for patients with heart disease.[29] This warning was based on a 10-year follow up study[30] to the CLARICOR trial[31] which showed a potential increase in risk of heart problems or death in patients with coronary heart disease occurring years after prescribing of a 2-week course of clarithromycin.[30] The hazard ratio for cardiovascular mortality was 1.42 (95% CI, 1.09-1.84; p=0.008), 1.24 (95% CI, 0.96-1.60; p=0.06), and 0.91 (95% CI 0.74-1.13: P=0.39) within 0-3 years, 3-6 years and 6-10 years, respectively. There is insufficient evidence to determine if this warning can be applied to patients without heart disease. This warning will continue to be monitored closely with post-marketing MedWatch submissions.

Loperamide

Another FDA drug safety warning addresses the safe use of over-the-counter (OTC) anti-diarrhea drug loperamide.[32] Loperamide blocks the *mu*-opioid receptors in the intestinal muscles to slow the movement in the intestines and decrease the number of bowel movements.[33] Recent reports have described the use of loperamide by consumers to treat the symptoms of opioid withdrawal at doses 40-100 times the recommended dose.[34] At these high doses, loperamide has caused QTc prolongation leading to Torsades de Pointes.[35] There is insufficient evidence to define the correlation between loperamide abuse and cardiac toxicity. In the 39 years since loperamide was approved, the FDA has received 48 cases of serious heart problems, most of which were reported after 2010. This is most likely due to the growing abuse or misuse of the product by patients to achieve a feeling of euphoria.[36] Due to this dangerous effect, health professionals are advised to recommend only the maximum approved daily dose for adults at 8 mg per day over the counter (OTC) dose and 16 mg per day for prescription use.[32]

- SGLT2 inhibitor safety alerts include Fournier's gangrene
- Evidence has demonstrated amputations with canagliflozin – it is unknown if this is a SGLT2 class effect
- Fluoroquinolone safety alerts include hypoglycemia, psychiatric events, and risk of aortic aneurysm/dissection
- Loperamide at high doses may cause QTc prolongation
- Clarithromycin use in existing heart disease causes

Conclusion

These safety warnings have brought attention to the possible harm related to use of the associated medications. The fluoroquinolone risk of hypoglycemia and psychiatric events have been added to the drug labels, as well as the risk of necrotizing fasciitis for SGLT2 inhibitors. The risk of aortic aneurysm with fluoroquinolones will be added to the prescribing information and medication guides, as required by the FDA. Ongoing safety assessments are still being conducted for risk of amputation in SGLT2 inhibitors and heart complications with clarithromycin. A higher level of evidence using randomized controlled trials is needed to confirm a clear association. Pharmacists and prescribing providers should be aware of the evolving evidence of safety for drugs after FDA approval.

Peer Reviewed by: Andrew Gibler, Pharm D, Director of Pharmacy Legacy Mount Hood Medical Center

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Benzodiazepine Safety and Tapering

Sarah Servid, Pharm.D., OSU Drug Use Research and Management Group

Benzodiazepines are commonly prescribed for a variety of mental health conditions. The Food and Drug Administration (FDA) labeled indications vary based on each specific benzodiazepine and include seizures, alcohol withdrawal, insomnia, panic disorder, anxiety, and adjunctive treatment of muscle spasms. They are also often used off-label for schizophrenia, depression, acute stress disorders, bipolar disorder, or agitation. In the United States, use of benzodiazepines has continued to increase, and it is estimated that over 7% of clinician visits are associated with prescription of a benzodiazepine.[1] However, despite common use, there is little evidence on efficacy and safety of long-term benzodiazepine use. This article briefly reviews evidence on safety of long-term use, describes interventions to deprescribe benzodiazepines, and provides resources for clinicians interested in tapering strategies.

Evidence and Guidance Against Long-term Use

There are limited controlled data available on long-term use of benzodiazepines, but many adverse events have been documented with long-term use. Controlled studies evaluating efficacy of benzodiazepines in mental health conditions were on average only 1 to 10 weeks in duration.[2] Similarly, there is little evidence of long-term benefit or evidence that benzodiazepines improve quality of life or function when used as a muscle relaxant for chronic pain.[3] Current guidelines from multiple societies recommend against use of benzodiazepines or recommend only short-term use for acute symptoms. For example, in patients with chronic low back pain, the Veterans Administration and Department of Defense (VA/DOD) guidelines recommend strongly against the use of chronic benzodiazepines as a muscle relaxant.[4] Only non-benzodiazepines muscle relaxants are recommended for short-term, acute pain.[4] Guidelines from National Institute for Health and Care Excellence (NICE) also recommend against use of benzodiazepines for muscle spasticity in patients with cerebral palsy, and only recommend diazepam as a third line agent in patients with spasticity due to multiple sclerosis.[5,6] Recent guidelines from the VA/DOD for post-traumatic stress disorder (PTSD) and acute stress reactions have a strong recommendation against the use of benzodiazepines (as monotherapy or combination therapy) for treatment of PTSD due to the lack of evidence supporting efficacy and known risks associated with treatment.[7] Similarly, guidelines from NICE for treatment of generalized anxiety disorder recommend against benzodiazepines except for short-term use during crisis.[8] For treatment of insomnia, first-line treatments include non-pharmacological modalities such as cognitive behavioral therapy.[9,10] Because insomnia often occurs as a result of other comorbid conditions, pharmacological treatment should address the underlying cause of insomnia. Pharmacotherapy (including benzodiazepines) is recommended only with intermittent dosing or short-term use (≤ 4 weeks) and only when first-line options have failed.[9,10] In the Oregon Health Plan (OHP), short-term use of zolpidem is the preferred sedative product for insomnia.

Safety Concerns with Benzodiazepines

Safety concerns with long-term benzodiazepines include risk for overdose, psychiatric instability, cognitive impairment, complications with pregnancy, and dependence or abuse. All benzodiazepines have a boxed warning for concomitant use with opioids.[11] Concomitant use can result in profound sedation, respiratory depression, coma and death. Evidence assessing the magnitude of risk associated with concomitant opioid and benzodiazepine prescribing is primarily based on observational data.[2] In 2 large retrospective cohort studies (n=5540), co-prescribing of these medications was associated with increased risk of drug-related deaths (adjusted hazard ratio [HR] 1.4; 95% CI 1.2 to 1.7 and HR 4.35; 95% CI 1.32 to 14.30).[2,12,13] Similarly, in 5 case series examining methadone overdose deaths (n=1127), blood toxicology was positive for both benzodiazepines and methadone in 36 to 67% of deaths.[2] Due to the retrospective nature of these data, the exact magnitude of risk associated with concomitant benzodiazepine and opioid administration is unclear. However, trends in combined opioid and benzodiazepine overdose remain of concern. Estimates from the National Institute on Drug Abuse indicate approximately 23% of opioid overdose deaths also tested positive for benzodiazepines.[14] Due to concerns associated with over-sedation, guidelines from both the Centers for Disease Control and 2016 Oregon Guidelines developed by the Chronic Pain Taskforce recommend against use of concomitant benzodiazepines and opioids (or other sedatives) whenever possible.[15,16] For patients on long-term therapy with both opioids and benzodiazepines, consider sequential tapers. Because rapid benzodiazepine tapers may be associated with more rebound anxiety or withdrawal symptoms, it is reasonable to consider an opioid taper first.[15]

Other adverse effects associated with benzodiazepine use include psychiatric or paradoxical reactions. Adverse events reported in postmarketing studies include acute hyperexcited states, irritability, aggression, hallucinations, psychoses, and sleep disturbances, and may occur more frequently in children or elderly patients.[17-19] Cognitive and memory impairment is another significant concern with long-term benzodiazepine use, and negative cognitive effects may persist for up to 6 months after discontinuation of the benzodiazepine.[9] Use of benzodiazepines has also been associated with emergence or worsening of pre-existing depression in postmarketing studies; use in patients with primary depressive disorder or psychosis is not recommended.[17] While rare, use of benzodiazepines (and other antiepileptic drugs) may be associated with an increased incidence of suicidal thoughts or behavior. In an analysis of 27,863 patients treated with 11 antiepileptic drugs including clonazepam, the estimated incidence of suicidal thoughts and behavior was approximately twice as high as placebo treated patients (0.43% vs. 0.24%; RR 1.8, 95% CI 1.2 to 2.7).[18] The estimated risk was similar upon comparison of clonazepam to other antiepileptic drugs.[18]

Patients who may have an increased risk for adverse events include elderly patients, patients who are pregnant, and those with concomitant respiratory disease or substance use disorders. Increased instability and sedation have been documented in patients over 65 years of age and Beer's Criteria recommends against use in this population.[20] Decreased clearance of benzodiazepines can occur in patients with impaired renal or hepatic function, and if treatment is necessary for these patients, the lowest effective dose for the shortest duration should be used.[17-19,21] In particular, benzodiazepines with active metabolites and longer duration of effect (e.g., diazepam and chlordiazepoxide) may be associated with increased drug accumulation or adverse effects in the elderly and should be avoided.[20] Risk of respiratory depression is also increased in patients with severe respiratory insufficiency such as chronic obstructive pulmonary disease (COPD) or sleep apnea syndrome, and benzodiazepines should only be prescribed when absolutely necessary for this population.[17-19] Benzodiazepines may also potentially cause fetal harm and congenital abnormalities during the first trimester, and while there are no well controlled studies in humans, congenital malformations have been documented in animal studies. Benzodiazepines should be avoided whenever possible or used with caution after an evaluation of risks and benefits of therapy in women who are pregnant or intending to become pregnant. Additionally, regular use in late pregnancy may increase the risk of withdrawal symptoms and complications for the infant after birth.[19] Symptoms such as hypothermia, muscle flaccidity, respiratory depression or apnea, and difficulty feeding have been documented in neonates born to mothers using benzodiazepines.[17,18,21] Benzodiazepines are classified by the Drug Enforcement Agency (DEA) as schedule IV substances and have been associated with abuse, misuse, and dependence.[17,19] Caution and monitoring are advised if prescribing benzodiazepines to patients with substance use disorders because of an increased predisposition to habituation and dependence. In Oregon, benzodiazepines are reported to the statewide prescription drug monitoring program (PDMP), and evaluation of the PDMP is recommended before prescribing for every patient.[22]

Risks with Benzodiazepine Withdrawal

Because of documented risks associated with benzodiazepine therapy and the lack of long-term efficacy data, periodic reassessment to evaluate ongoing need for therapy and current risks with treatment is recommended for all patients prescribed long-term benzodiazepines. If risks of therapy outweigh benefits, gradual dose reduction is recommended for patients on established long-term therapy. Benzodiazepines are associated with physical dependence and discontinuation (particularly abrupt discontinuation) may be associated with significant adverse effects including rebound, withdrawal, and symptom recurrence.[19,21] Rebound symptoms refer to the recurrence of symptoms at a greater severity than observed at baseline. The exact incidence of withdrawal or rebound symptoms with benzodiazepine discontinuation is unclear, and more frequent symptoms may occur in patients prescribed higher doses or longer-term therapy.[19,21] For example, discontinuation symptoms occurred more frequently or with greater severity in patients prescribed more than 4 mg/day of alprazolam or prescribed diazepam for longer periods.[19,21]

In a clinical trial evaluating alprazolam discontinuation in 63 patients with panic disorder, common withdrawal symptoms included heightened sensory perception, impaired concentration, and muscle cramps.[21] Severe withdrawal symptoms with benzodiazepines can include seizures, though the exact incidence of severe symptoms is unclear. Of the 1980 patients treated with alprazolam during clinical trials, seizures were observed in 8 patients after drug discontinuation (5 of which occurred after abrupt dose reduction or discontinuation).[21] The risk of seizures with alprazolam appear to be greatest in the 24 to 72 hours after discontinuation.[21] Similar withdrawal symptoms have been documented in post-marketing studies of other benzodiazepines, but there is little data comparing incidence or severity of withdrawal symptoms between agents.

Benzodiazepine Taper Strategies

In patients prescribed benzodiazepines for mental health conditions or insomnia, gradual dose reduction can significantly decrease risk of withdrawal symptoms. However, there is little evidence available on the optimal duration or rate of tapering and no evidence which indicates a single tapering strategy may be more successful than another. Guidelines from the VA/DOD provide the following recommendations for patients with sedative hypnotic use disorder stabilization and withdrawal:[23]

- Gradual taper the original benzodiazepine OR
- Substitute a longer-acting benzodiazepine (diazepam or chlordiazepoxide) then taper OR
- Substitute phenobarbital for the addicting agent and taper gradually

The optimal rate and type of taper strategy may vary between patients and should be tailored based on patient experience and current benzodiazepine dose. In clinical studies of clonazepam, patients with short-term use for treatment of panic disorder (6-9 weeks) were tapered over 7 weeks with dose reductions of 0.125 mg twice daily every 3 days until the drug was completely withdrawn.[18] While there is no evidence to accurately estimate the risk of withdrawal symptoms in patients on long-term benzodiazepine use, more gradual tapers may be required for patients on higher doses or those with longer use. Because early withdrawal symptoms are often better tolerated than later withdrawal symptoms, taper strategies may begin with a more rapid early dose reduction followed by a slower taper.[23] For patients on low dose benzodiazepines, an initial reduction of up to 20% weekly may be initially considered with more gradual reductions over time.[15,23] Patients on higher doses of benzodiazepines (e.g., those approaching the FDA-approved maximum daily dose) will likely require a longer taper period over 2 to 6 months.[23] One common taper strategy in patients on high dose benzodiazepines is a weekly 25% dose reduction over 2 weeks until 50% of the dose remains then further reduction by 1/8 (~12%) every week.[23] Because rebound or withdrawal symptoms may occur with rapid dose reduction, periodic monitoring is recommended with adjustments to slow the taper plan if needed.[23]

Transitioning to a longer-acting benzodiazepine is another strategy which is intended to minimize fluctuations in drug levels over time. The approximate equivalent doses of common benzodiazepines are shown in **Table. 1**. Both chlordiazepoxide and diazepam have active metabolites with extended half-lives, and use of these agents may provide more consistent drug levels, and potentially fewer withdrawal symptoms, as the patient is tapered.[23] However, both diazepam and chlordiazepoxide are excreted in the urine, and this strategy may not be an optimal choice for elderly patients or those with renal impairment due to an increased risk of drug accumulation.

Table 1. Common Benzodiazepine Conversions[23]

Drug	Approximate Equivalent Dose	Time to Peak plasma level (hours)	Half-life (in hours for parent drug)	Metabolic activity (maximal half-life in hours)
Alprazolam	1 mg	1-2	12 ± 2	Inactive
Chlordiazepoxide	25 mg	1-4	10 ± 4	Active (up to 120 hours)
Clonazepam	1 mg	1-4	23 ± 5	Inactive
Diazepam	10 mg	2-4	43 ± 13	Active (up to 120 hours)
Lorazepam	2 mg	1-2	14 ± 5	Inactive
Phenobarbital	30 mg	1+	53-140	Inactive

Substitution therapies have been used to try to mitigate withdrawal symptoms and facilitate deprescribing, but benefit with these therapies remains unclear. Guidelines from the VA/DOD suggest offering pharmacological substitution with phenobarbital as an option to facilitate discontinuation of benzodiazepines based on low quality evidence.[23] The daily benzodiazepine dose is converted to a phenobarbital equivalent and divided into 3 doses per day for two days.[23] Beginning on day 3, phenobarbital is reduced by 30 mg per day.[23] Other drugs studied for benzodiazepine discontinuation included valproate, pregabalin, tricyclic antidepressants, paroxetine, carbamazepine and flumazenil. [24] Evidence for these therapies is overall insufficient to low quality due to small sample sizes of available studies (n=18 to 144), notable risk of bias, and significant heterogeneity which limits confidence in any findings.[24]

Patient education and cognitive behavioral therapy are recommended in conjunction with benzodiazepine tapers and have demonstrated improved success with complete benzodiazepine discontinuation compared to tapering alone.[15,23] In a Cochrane review of tapering strategies for benzodiazepines (n=575), use of cognitive behavioral therapy in addition to a tapering regimen resulted in a higher rate of successful discontinuation at 2-3 months follow-up compared to a taper alone (58.9% vs. 41.5%; ARR 17.4%; RR 1.51, 95% CI 1.15 to 1.98; moderate quality evidence).[25] While the long-term effects of cognitive behavioral therapy on benzodiazepine use are less clear, use in the short-term may help patients develop positive behaviors and coping strategies during the taper process.[25]

Additional Resources

Multiple resources are available for both providers and pharmacists to assist with developing taper plans and discussing tapering with patients.

- Clinician resources and clinical pearls from the VA/DOD for tapering benzodiazepines in patients where risks outweigh benefits (e.g., patients with PTSD)[26]
- The Canadian Family Physicians guidelines for tapering patients using benzodiazepines for insomnia[27]
- The College of Psychiatric and Neurologic Pharmacists toolkit for tapering benzodiazepines[28]

OHP Policy

In the OHP, most benzodiazepines (with the exception of clonazepam) are paid for by fee-for-service rather than coordinated care organizations. Due to the lack of long-term efficacy and known safety concerns, a prior authorization is required for use of benzodiazepines beyond 4 weeks. Requests for treatment of mental health conditions must document trial or failure of first-line treatment options and rationale to support long-term use. Use for PTSD or use

in combination with other sedating medications is not recommended. For patients in which the risks of therapy outweigh the benefits, providers should consider a taper plan for their patient.

> For OHP patients starting benzodiazepine treatment, prior authorization is required for durations of more than 4 weeks.

More information on these treatment options, along with other therapeutic reviews, can be found on the Oregon Health Plan fee-for-service searchable preferred drug list at http://www.orpdl.org/drugs/.

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Drug Use Evaluation: Combination Biologic Therapy for Immunologic Conditions

Research Questions:

- How many patients receiving biologic therapy for immunologic conditions are also prescribed concomitant disease modifying rheumatologic arthritic drugs (DMARDs)?

Conclusions:

- In patients with psoriatic or rheumatoid arthritis for which combination therapy with a DMARD and biologic is recommended, combination therapy was prescribed for only 39 patients (less than 35% of patients with these diagnoses). Thirty-two patients with a diagnosis of psoriatic arthritis and 48 patients with rheumatoid arthritis were not prescribed combination therapy.
- In patients prescribed a concomitant DMARD, adherence to DMARD therapy was low. Approximately 28% of patients had PDC less than 25% over 6 months for a DMARD indicating either only short-term use or low adherence to continuous therapy.
- A recent Food and Drug Administration (FDA) safety alert for tofacitinib describes an increased risk of pulmonary embolism and death in patients with rheumatoid arthritis prescribed more than the FDA-recommended maximum dose of 5 mg twice daily.

Recommendations:

- Current utilization data supports inclusion of concomitant DMARD use in PA criteria when appropriate (see **Appendix 1**).
- Update prior authorization (PA) criteria to include a maximum dose for patients with rheumatoid arthritis prescribed tofacitinib and to reinforce periodic tuberculosis testing.

Background and Purpose of the Review:

Biologics for autoimmune conditions are used for a wide variety of conditions. PA criteria are required for all biologic treatments, and current criteria recommend use of a DMARDs as a first-line treatment for most conditions. Recently, PA criteria were updated to include evaluation of concomitant DMARD and biologic therapy for rheumatoid arthritis and psoriatic arthritis. Guidelines from the National Institute of Care Excellence (NICE) recommend use of concomitant DMARDs (primarily methotrexate) in combination with biologic therapy for patients with psoriatic arthritis or rheumatoid arthritis. Combination therapy with DMARDs and biologics is not recommended for juvenile idiopathic arthritis, ankylosing spondylitis, plaque psoriasis, or ulcerative colitis.[1,2] Similar recommendations are made in the 2016 guidelines from the European League Against Rheumatism which recommend use of biologics or targeted synthetic DMARD in combination with a DMARD for patients with rheumatoid arthritis.[2]

This brief drug use evaluation quantifies the proportion of patients prescribed combination biologic and DMARD therapy and evaluates adherence to those therapies based on available claims data. A new safety communication from the FDA will also be reviewed.

New FDA Safety Communications

In March 2019, the FDA issued a safety communication regarding risk of adverse effects with 10 mg twice daily tofacitinib in patients with rheumatoid arthritis.[3] The maximum dose of tofacitinib in patients with rheumatoid arthritis is 5 mg twice daily, and the higher dose is only approved for patients with ulcerative colitis. The warning was issued after a safety clinical trial found an increased risk of pulmonary embolism and death in patients prescribed 10 mg twice daily for rheumatoid arthritis compared to a lower tofacitinib dose or a tumor necrosis factor inhibitor.[3] This post-marketing safety trial was evaluating 5 and 10 mg twice daily doses of tofacitinib in combination with methotrexate. Patients included in the study were at least 50 years old and had at least one cardiovascular risk factor. Patients enrolled in the trial on a 10 mg twice daily dose of tofacitinib are being transitioned to a lower dose, and the trial is expected to be complete by the end of 2019.[3]

Methods:

The patient population included current Medicaid patients with a fee for service (FFS) claim for a biologic for autoimmune conditions from 7/01/2017 to 6/30/2018. The index event was defined as the first paid pharmacy or medical claim for a biologic listed in **Appendix 2 (Table A1)**. Patients on combination therapy were defined as any patient with paid claims for at least 21 days of overlapping therapy for both a DMARD and biologic in the 6 months following the index event with no more than a 7 day gap in coverage. DMARDs of interest are listed in **Appendix 2**. Results were stratified by drug and patient diagnoses. Patients with diagnoses for relevant conditions were identified based on ICD-10 codes within the year before or 6 months after the index event (**Appendix 2**). Adherence to individual and combination therapy was evaluated using the proportion of days covered by both therapies (biologic and DMARD) in the 6 months following the index event. Days' supply for pharmacy claims was defined based on information submitted with the claim, and days' supply for medical claims was defined based on maintenance dose for each agent (**Appendix 2**). If maintenance dose varied by condition, the longest estimate of days' supply was used to provide a more conservative estimate of treatment adherence.

The total number of patients with dual biologic treatment was also evaluated using the same definitions listed above. Adherence to combination biologic treatment was evaluated using the proportion of days covered by both biologics in the 6 months following the index event.

Patients were excluded if they had Medicare part D coverage, Medicare Part B coverage and medical claims for a biologic, or had ≤75% Medicaid eligibility in the year prior to the index event.

Results:

Of the nearly 250 patients prescribed biologics over the course of the study year, less than half of patients had a diagnosis of rheumatoid or psoriatic arthritis for which combination therapy with a DMARD is recommended (**Table 1**). Of all patients prescribed a biologic for any condition, only 23% of patients (n=58) were prescribed combination treatment with a biologic and DMARD. In patients with psoriatic or rheumatoid arthritis, combination therapy was prescribed for only 39 patients (less than 35% of patients with these diagnoses). Claims indicate that combination treatment was not prescribed for 32 patients with psoriatic arthritis or 48 patients with rheumatoid arthritis.

Overall adherence to DMARD therapy was low (**Table 2**). Only 26-28% of patients had a PDC of more than 75% for DMARD therapy indicating high adherence to continuous therapy. Approximately 28% of patients had PDC less than 25% over 6 months for a DMARD indicating either only short-term use or low adherence to continuous therapy.

Table 1. Assessment of combination treatment in the 6 months following the first paid biologic claim. Results are presented for the total population then stratified by the index event drug and by relevant diagnosis present in the 1 year before or 6 months after the IE. If patients had multiple diagnoses, they may be counted more than once.

	Patients with Combination Treatment		No Combination Treatment	
	#	%	#	%
Total	58		190	
Individual Drugs				
abatacept	1	1.7%	1	0.5%
abatacept/maltose	2	3.4%	1	0.5%
adalimumab	19	32.8%	37	19.5%
apremilast	0	0.0%	6	3.2%
belimumab	0	0.0%	2	1.1%
certolizumab pegol	0	0.0%	8	4.2%
etanercept	11	19.0%	31	16.3%
golimumab	3	5.2%	4	2.1%
infliximab	12	20.7%	44	23.2%
infliximab-dyyb	1	1.7%	0	0.0%
natalizumab	1	1.7%	7	3.7%
rituximab	3	5.2%	20	10.5%
secukinumab	1	1.7%	2	1.1%
tocilizumab	3	5.2%	6	3.2%
tofacitinib citrate	1	1.7%	3	1.6%
ustekinumab	0	0.0%	9	4.7%
vedolizumab	0	0.0%	9	4.7%
Diagnosis				
Ankylosing spondylitis	2	3.4%	10	5.3%
Crohn's Disease	8	13.8%	47	24.7%
Juvenile Idiopathic Arthritis	1	1.7%	7	3.7%
Plaque psoriasis	8	13.8%	48	25.3%
Psoriatic arthritis	6	10.3%	32	16.8%
Rheumatoid Arthritis	34	58.6%	48	25.3%
Ulcerative colitis	4	6.9%	18	9.5%
None of the above	5	8.6%	31	16.3%

Table 2. Adherence to combination treatment evaluated as the proportion of days covered by both a DMARD and biologic treatment in the 6 months following the index event.

	All Patients with Combination Treatment		Subgroup of patients with diagnosis of psoriatic arthritis or rheumatoid arthritis on combination therapy	
	#	%	#	%
N=	58		39	
Biologic				
PDC <=25%	3	5.2%	3	7.7%
PDC 26-75%	33	56.9%	20	51.3%
PDC >75%	22	37.9%	16	41.0%
DMARD				
PDC <=25%	16	27.6%	11	28.2%
PDC 26-75%	26	44.8%	18	46.2%
PDC >75%	16	27.6%	10	25.6%
Combination				
PDC <=25%	34	58.6%	24	61.5%
PDC 26-75%	20	34.5%	12	30.8%
PDC >75%	4	6.9%	3	7.7%

Data Limitations:

Diagnosis and proportion of covered days are based on claims history which may not accurately reflect true patient diagnoses or correlate with actual medication adherence. Medical claims are not submitted with a days' supply and duration of therapy based on medical claims is an estimate only. Days' supply estimates were based on maintenance dosing for biologics and may not be accurate if members are initiating treatment. Similarly, estimates of days' supply based on pharmacy claims may be inaccurate if they are inappropriately billed and may not correlate to actual adherence for the patient.

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Biologics for Autoimmune Diseases

Goal(s):

- Restrict use of biologics to OHP funded conditions and according to OHP guidelines for use.
- Promote use that is consistent with national clinical practice guidelines and medical evidence.
- Promote use of high value products.

Length of Authorization:

- Up to 12 months

Requires PA:

- All biologics for autoimmune diseases (both pharmacy and physician-administered claims)

Covered Alternatives:

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

Table 1. Approved and Funded Indications for Biologic Immunosuppressants.

Drug Name	Ankylosing Spondylitis	Crohn's Disease	Juvenile Idiopathic Arthritis	Plaque Psoriasis	Psoriatic Arthritis	Rheumatoid Arthritis	Ulcerative Colitis	Other
Abatacept (ORENCIA)			≥2 yo		≥18 yo	≥18 yo		
Adalimumab (HUMIRA) and biosimilars	≥18 yo	≥6 yo (Humira) ≥18 yo (biosimilars)	≥2 yo(Humira) ≥4 yo (biosimilars)	≥18 yo	≥18 yo	≥18 yo	≥18 yo	Uveitis (non-infectious) ≥2 yo (Humira)
Anakinra (KINERET)						≥18 yo		NOMID
Apremilast (OTEZLA)				≥18 yo	≥18 yo			
Baricitinib (OLUMIANT)						≥18 yo		
Broadalumab				≥18 yo				

(SILIQ)								
Canakinumab (ILARIS)			≥2 yo					FCAS ≥4 yo MWS ≥4 yo TRAPS ≥ 4yo HIDS≥ 4 yo MKD≥ 4 yo FMF≥ 4 yo
Certolizumab (CIMZIA)	≥18 yo	≥18 yo		≥18 yo	≥18 yo	≥18 yo		
Etanercept (ENBREL) and biosimilars	≥18 yo		≥2 yo	≥4 yo (Enbrel) ≥18 yo (biosimilars)	≥18 yo	≥18 yo		
Golimumab (SIMPONI and SIMPONI ARIA)	≥18 yo				≥18 yo	≥18 yo	≥18 yo (Simponi)	
Guselkumab (Tremfya)				≥18 yo				
Infliximab (REMICADE) and biosimilars	≥18 yo	≥6 yo		≥18 yo	≥18 yo	≥18 yo	≥6 yo (Remicade) ≥18 yo (biosimilars)	
Ixekizumab (TALTZ)				≥18 yo	≥18 yo			
Rituximab (RITUXAN)						≥18 yo		CLL ≥18 yo NHL ≥18 yo GPA ≥18 yo Pemphigus Vulgaris ≥18 yo
Sarilumab (KEVZARA)						≥18 yo		
Secukinumab (COSENTYX)	≥18 yo			≥18 yo	≥18 yo			
Tildrakizumab-asmn (ILUMYA)				≥18 yo				
Tocilizumab (ACTEMRA)			≥2 yo			≥18 yo		CRS ≥2 yo GCA ≥18 yo
Tofacitinib (XELJANZ)					≥18 yo	≥18 yo	≥18 yo	
Ustekinumab (STELARA)		≥ 18 yo		≥12 yo	≥18 yo			
Vedolizumab (ENTYVIO)		≥18 yo					≥18 yo	

Abbreviations: CLL = Chronic Lymphocytic Leukemia; CRS = Cytokine Release Syndrome; FCAS = Familial Cold Autoinflammatory Syndrome; FMF = Familial Mediterranean Fever; GCA = Giant Cell Arteritis; GPA = Granulomatosis with Polyangiitis (Wegener's Granulomatosis); HIDS: Hyperimmunoglobulin D Syndrome; MKD = Mevalonate Kinase

Deficiency; MWS = Muckle-Wells Syndrome; NHL = Non-Hodgkin's Lymphoma; NOMID = Neonatal Onset Multi-Systemic Inflammatory Disease; TRAPS = Tumor Necrosis Factor Receptor Associated Periodic

Syndrome; yo = years old.

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. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #4
4. Is the request for a non-preferred product and will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics Committee.	**Yes:** Inform prescriber of preferred alternatives.	**No:** Go to #5
5. Has the patient been annually screened for latent or active tuberculosis and if positive, started tuberculosis treatment?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness. May approve for up to 3 months to allow time for screening.

Approval Criteria		
6. Is the diagnosis Juvenile Idiopathic Arthritis, non-Hodgkin Lymphoma, Chronic Lymphocytic Leukemia, Non-infectious Posterior Uveitis, or one of the following syndromes: • Familial Cold Autoinflammatory Syndrome • Muckel-Wells Syndrome • Neonatal Onset Multi-Systemic Inflammatory Disease • Tumor Necrosis Factor Receptor Associated Periodic Syndrome • Hyperimmunoglobulin D Syndrome • Mevalonate Kinase Deficiency • Familial Mediterranean Fever • Giant Cell Arteritis • Cytokine Release Syndrome AND Is the request for a drug FDA-approved for one of these conditions as defined in Table 1?	**Yes:** Approve for length of treatment.	**No:** Go to #7
7. Is the diagnosis ankylosing spondylitis and the request for a drug FDA-approved for this condition as defined in Table 1?	**Yes:** Go to #8	**No:** Go to #9
8. If the request is for a non-preferred agent, has the patient failed to respond or had inadequate response to a Humira® product or an Enbrel® product after a trial of at least 3 months?	**Yes:** Approve for up to 6 months. Document therapy with dates.	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
9. Is the diagnosis plaque psoriasis and the request for a drug FDA-approved for this condition as defined in Table 1? Note: Only treatment for *severe* plaque psoriasis is funded by the OHP.	**Yes:** Go to #10	**No**: Go to #12
10. Is the plaque psoriasis severe in nature, which has resulted in functional impairment (e.g., inability to use hands or feet for activities of daily living, or significant facial involvement preventing normal social interaction) and one or more of the following: • At least 10% body surface area involvement; or • Hand, foot or mucous membrane involvement?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; not funded by the OHP.
11. Has the patient failed to respond or had inadequate response to each of the following first-line treatments: • Topical high potency corticosteroid (e.g., betamethasone dipropionate 0.05%, clobetasol propionate 0.05%, fluocinonide 0.05%, halcinonide 0.1%, halobetasol propionate 0.05%; triamcinolone 0.5%); and • At least one other topical agent: calcipotriene, tazarotene, anthralin; and • Phototherapy; and • At least one other systemic therapy: acitretin, cyclosporine, or methotrexate; and • One biologic agent: either a Humira® product or an Enbrel® product for at least 3 months?	**Yes**: Approve for up to 6 months. Document each therapy with dates.	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
12. Is the diagnosis rheumatoid arthritis or psoriatic arthritis and the request for a drug FDA-approved for these conditions as defined in Table 1?	**Yes:** Go to #13	**No:** Go to #17
13. Has the patient failed to respond or had inadequate response to at least one of the following medications: • Methotrexate, leflunomide, sulfasalazine or hydroxychloroquine for ≥ 6 months; or • Have a documented intolerance or contraindication to disease-modifying antirheumatic drugs (DMARDs)? AND • Had treatment failure with at least one biologic agent: a Humira® product or an Enbrel® product for at least 3 months?	**Yes:** Go to #14 Document each therapy with dates. If applicable, document intolerance or contraindication(s).	**No:** Pass to RPh. Deny; medical appropriateness.
14. Is the request for tofacitinib?	**Yes:** Go to #16	**No:** Go to #15
15. Is the patient on concurrent DMARD therapy with plans to continue concomitant use OR does the patient have documented intolerance or contraindication to DMARDs?	**Yes:** Approve for up to 6 months.	**No:** Pass to RPh. Deny; medical appropriateness. Biologic therapy is recommended in combination with DMARDs (e.g. methotrexate) for those who have had inadequate response with DMARDs.

Approval Criteria		
16. Is the patient currently on other biologic therapy or on a potent immunosuppressant like azathioprine, tacrolimus or cyclosporine? Note: Tofacitinib may be used concurrently with methotrexate or other oral DMARD drugs.	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve for up to 6 months at a maximum dose of 10 or 11 mg daily for Rheumatoid Arthritis OR~~.~~ 10 mg twice daily for 8 weeks then 5 or 10 mg twice daily for Ulcerative Colitis
17. Is the diagnosis Crohn's disease or ulcerative colitis and the request for a drug FDA-approved for these conditions as defined in Table 1?	**Yes:** Go to #18	**No:** Go to #19
18. Has the patient failed to respond or had inadequate response to at least one of the following conventional immunosuppressive therapies for ≥6 months: • Mercaptopurine, azathioprine, or budesonide; or • Have a documented intolerance or contraindication to conventional therapy? AND • Has the patient tried and failed a 3 month trial of a Humira® product?	**Yes:** Approve for up to 12 months. Document each therapy with dates. If applicable, document intolerance or contraindication(s).	**No:** Pass to RPh. Deny; medical appropriateness.
19. Is the diagnosis Granulomatosis with Polyangiitis or Microscopic Polyangiitis and the requested drug rituximab for *induction or maintenance* of remission?	**Yes:** Approve for length of treatment.	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the request for treatment of psoriatic arthritis or rheumatoid arthritis?	**Yes:** Go to #2	**No:** Go to #3
2. Has the patient been adherent to both biologic and DMARD therapy?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Has the patient's condition improved as assessed by the prescribing physician and physician attests to patient's improvement.	**Yes:** Approve for 6 months. Document baseline assessment and physician attestation received.	**No:** Pass to RPh; Deny; medical appropriateness.

P&T/DUR Review: *1/19 (DM); 1/18; 7/17; 11/16; 9/16; 3/16; 7/15; 9/14; 8/12*
Implementation: *3/1/19; 3/1/18; 9/1/17; 1/1/17; 9/27/14; 2/21/13*

Appendix 2. Coding Information

Table A1. Coding for biologics and DMARDs

Category	HSN	Generic
Biologics for Autoimmune Conditions	037825	abatacept
Biologics for Autoimmune Conditions	033411	abatacept/maltose
Biologics for Autoimmune Conditions	024800	adalimumab
Biologics for Autoimmune Conditions	022953	anakinra
Biologics for Autoimmune Conditions	040967	apremilast
Biologics for Autoimmune Conditions	044296	baricitinib
Biologics for Autoimmune Conditions	037462	belimumab
Biologics for Autoimmune Conditions	044102	brodalumab
Biologics for Autoimmune Conditions	036497	canakinumab/PF
Biologics for Autoimmune Conditions	035554	certolizumab pegol
Biologics for Autoimmune Conditions	018830	etanercept
Biologics for Autoimmune Conditions	036278	golimumab
Biologics for Autoimmune Conditions	044418	guselkumab

Biologics for Autoimmune Conditions	018747	infliximab
Biologics for Autoimmune Conditions	044432	infliximab-abda
Biologics for Autoimmune Conditions	043249	infliximab-dyyb
Biologics for Autoimmune Conditions	043193	ixekizumab
Biologics for Autoimmune Conditions	026750	natalizumab
Biologics for Autoimmune Conditions	016848	rituximab
Biologics for Autoimmune Conditions	044183	sarilumab
Biologics for Autoimmune Conditions	041715	secukinumab
Biologics for Autoimmune Conditions	044823	tildrakizumab-asmn
Biologics for Autoimmune Conditions	036466	tocilizumab
Biologics for Autoimmune Conditions	039768	tofacitinib citrate
Biologics for Autoimmune Conditions	036187	ustekinumab
Biologics for Autoimmune Conditions	036187	ustekinumab
Biologics for Autoimmune Conditions	041146	vedolizumab
Systemic DMARDs	004523	azathioprine
Systemic DMARDs	004524	cyclosporine
Systemic DMARDs	010086	cyclosporine, modified
Systemic DMARDs	007827	acitretin
Systemic DMARDs	003906	methotrexate
Systemic DMARDs	003905	methotrexate sodium
Systemic DMARDs	024819	methotrexate sodium/PF
Systemic DMARDs	040683	methotrexate/PF
Systemic DMARDs	004074	sulfasalazine
Systemic DMARDs	004151	hydroxychloroquine sulfate
Systemic DMARDs	018694	leflunomide
Systemic DMARDs	003908	mercaptopurine

Table A2. Diagnosis Codes for relevant conditions of interest

Condition	**ICD-10 Diagnosis Codes**
Ankylosing spondylitis	M45xxx
Crohn's Disease	K50xxx
Juvenile Idiopathic Arthritis	M08xxx
Plaque psoriasis	L400x-L404x, L408x, L409x
Psoriatic arthritis	L405x
Rheumatoid Arthritis	M05xxx, M06xxx
Ulcerative colitis	K51xxx

Table A3. Days' Supply Estimates for Medical Claims

Procedure Code	Drug Name	Procedure Description	Days' Supply
C9026	vedolizumab	Injection, Vedolizumab, 1 Mg	56 days
C9029	guselkumab	Injection, Guselkumab, 1 Mg	56 days
C9487	ustekinumab	Ustekinumab, For Intravenous Injection, 1 Mg	56 days
J0129	abatacept	Injection, Abatacept, 10 Mg (Code May Be Used For Medicare When Drug Administered Under The Direct S	7 days
J0129	abatacept/maltose	Injection, Abatacept, 10 Mg (Code May Be Used For Medicare When Drug Administered Under The Direct S	28 days
J0135	adalimumab	Injection, Adalimumab, 20 Mg	14 days
J0490	belimumab	Injection, Belimumab, 10 Mg	28 days
J0638	canakinumab/PF	Injection, Canakinumab, 1 Mg	28 days
J0717	certolizumab pegol	Injection, Certolizumab Pegol, 1 Mg (Code May Be Used For Medicare When Drug Administered Under The	28 days
J0718	certolizumab pegol	Injection, Certolizumab Pegol, 1 Mg	28 days
J1438	etanercept	Injection, Etanercept, 25 Mg (Code May Be Used For Medicare When Drug Administered Under The Direct	7 days
J1602	golimumab	Injection, Golimumab, 1 Mg, For Intravenous Use	56 days
J1745	infliximab	Injection, Infliximab, Excludes Biosimilar, 10 Mg	56 days
J2323	natalizumab	Injection, Natalizumab, 1 Mg	28 days
J3262	tocilizumab	Injection, Tocilizumab, 1 Mg	28 days
J3357	ustekinumab	Ustekinumab, For Subcutaneous Injection, 1 Mg	84 days
J3358	ustekinumab	Ustekinumab, For Intravenous Injection, 1 Mg	56 days
J3380	vedolizumab	Injection, Vedolizumab, 1 Mg	56 days
J9310	rituximab	Injection, Rituximab, 100 Mg	168 days
J9312	rituximab	Injection, Rituximab, 10 Mg	168 days
Q2044	belimumab	Injection, Belimumab, 10 Mg	28 days
Q4079	natalizumab	Injection, Natalizumab, 1 Mg	28 days
Q5102	infliximab-abda	Injection, Infliximab, Biosimilar, 10 Mg	56 days
Q5102	infliximab-dyyb	Injection, Infliximab, Biosimilar, 10 Mg	56 days
Q5103	infliximab-dyyb	Injection, Infliximab-Dyyb, Biosimilar, (Inflectra), 10 Mg	56 days
Q5104	infliximab-abda	Injection, Infliximab-Abda, Biosimilar, (Renflexis), 10 Mg	56 days
Q9989	ustekinumab	Ustekinumab, For Intravenous Injection, 1 Mg	56 days

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Drug Use Evaluation: Attention Deficit Hyperactive Disorder Utilization in Adults

Research Questions:

- How have prescribing patterns, utilization and dosages of Attention Deficit Hyperactive Disorder (ADHD) medications in adults enrolled in Oregon Health Plan changed over time?
- How many adults taking ADHD medications have a diagnosis of ADHD or other Food and Drug Administration (FDA) approved indication for use?
- What proportion of adults on ADHD medications have a history of substance use disorder?
- What is the incidence of Emergency Department (ED) visits and/or hospitalizations due to drug overdose in this patient population?
- What is the prevalence of concurrent use of ADHD medications and opioids in adults with ADHD?

Conclusions:

- Utilization of ADHD medications in adults has increased 216% from 2014 to 2018 in per member per month (PMPM) per thousand (4.16 PMPM x 1000 to 13.15 PMPM x 1000 in 2018) see **Figure 3.**
- Approximately 42% of adults on ADHD medications have a diagnosis of ADHD based on available medical claims. However, a significant portion of patients (36%) do not have an ADHD diagnosis reported in claims data. Off-label use accounts for approximately 17% of claims.
- A significant proportion of adults prescribed ADHD medication have a diagnosis suggesting concurrent substance or alcohol abuse/dependence (36%).
- The proportion of patients with a hospitalizations due to drug or alcohol overdose was low (1%). Based on available claims data, there does not seem to be a safety concern for medical visits due to drug or alcohol overdose in adults prescribed ADHD medications.
- A small proportion of patients have concurrent use of ADHD medications and opioids (0.9%).

Recommendations:

- Continue to monitor use of ADHD medications in the adult population and evaluate trends in adults.
- Consider provider education on importance of diagnosis and assessment for patients with treatment-resistant ADHD symptoms and those at an increased risk of substance misuse.

Background:

Attention-Deficit Hyperactivity Disorder (ADHD) is a neurobehavioral disorder affecting over 11% of school-aged children according to 2011 Center for Disease and Prevention Control (CDC) data.[1] Traditionally, ADHD has been thought of as a childhood disorder, although symptoms may persist into adulthood for many individuals, and require lifelong treatment for some patients.[2] It is estimated that ADHD affects approximately 3 to 4% of adults worldwide.[2, 3] The CDC recommends the following criteria are met in adults for diagnosis of ADHD: 1) several symptoms were present before 12 years of age, 2) several symptoms are

present in 2 or more settings, 3) clear evidence that the symptoms interfere with, or reduce the quality of work functioning, and 4) the symptoms are not better explained by another mental disorder and do not happen only during the course of another psychotic disorder.[1]

Stimulant medications used for treatment of ADHD include methylphenidates and amphetamines in addition to non-stimulants such as atomoxetine. The 2018 National Institute for Health and Care Excellence (NICE) guidelines suggest lisdexamfetamine or methylphenidate as first-line pharmacological agents for adults with ADHD.[4] Atomoxetine is recommended as second line therapy for people that cannot tolerate stimulants or if they do not respond after 6 weeks of therapy.[4] Untreated or sub-optimally treated adults may be subjected to executive functioning deficits which reduce overall quality of life such as inability to complete tasks or prioritize projects.[2, 3] Adult ADHD is associated with a high prevalence of comorbidities causing personal suffering and maladaptations. Co-morbid mood disorder, anxiety, obsessive compulsive disorder, personality disorder, learning disabilities, and drug and alcohol abuse have frequently been reported in combination with ADHD in adults.[5] Failing to treat ADHD in adults can result in symptom intensity that is linked with criminality, abuse, and other psychiatric problems.[6] There is very little data on treatment effectiveness of ADHD with central nervous system (CNS) stimulants in adults, and more research is need to understand the potential benefits of treatment.[3] Low quality evidence from a Cochrane review showed that amphetamine use in adults improved the severity of ADHD symptoms in the short term, but did not improve retention to treatment or any other long term outcomes of efficacy and safety.[7] There was no evidence that higher doses of amphetamines were more efficacious than lower ones, and amphetamines were also associated with higher attrition due to adverse events compared to placebo.[6]

A growing concern is the misuse and abuse of stimulant medications in adults. A systematic review found that the number of adult emergency department (ED) visits related to nonmedical use of prescription stimulants rose nearly 200% from 5,212 in 2005 to 15,585 in 2010.[8] In another study, when 12,000 respondents diagnosed with ADHD were surveyed, 9.2% had lied about symptoms to motivate a doctor to prescribe ADHD medications and 19.1% intentionally took more ADHD medication than prescribed.[8] Additionally, 18.1% modified their ADHD medication, including taking the medication by chewing, dissolving, snorting, smoking or injection.[8] A 2016 national patient survey on drug use found that the motivation for stimulant misuse in adults over 18 years of age was improved concentration (56.3%), assistance with studying (21.9%), to achieve a high or other drug effects (15.5%), or for weight loss (4.1%).[9] This study also found the prevalence of stimulant misuse without diagnosis of substance use disorder was higher among adults with Medicaid, than those with private insurance only.[9] There is a limited body of clinical evidence when assessing the risks of using stimulant medications in patients with SUD, however it is known that the risk of untreated ADHD is linked to drug and alcohol abuse meaning potentially, treating with stimulants may outweigh the risk. A cross sectional study in over 65,000 adults in Medicaid found that the prevalence of ADHD increased from 2.20 per 1,000 patients in 1999, to 10.57 in 2010.[10] Similarly, the prevalence of ADHD treatment increased from 1.95 per 1,000 patients in 1999 to 13.16 in 2010.[10] The increase in diagnosis of ADHD may possibly be attributed to the modified diagnostic criteria among adults over time which included additional behaviors and core symptoms. Interestingly, amphetamine salts were the most utilized ADHD treatment, and atomoxetine was on the decline across the 29 states included in the study. In patients with an ADHD diagnosis, approximately half of patients did not have a prescription claim within 6 months of the diagnosis. Comparatively, half of patients on ADHD medications did not have a diagnosis in the 6 months before the treatment.[10] This confirms previous evidence that ADHD is commonly untreated, while also demonstrating that stimulants are often prescribed without diagnosis.[10] One limitation of this is the findings were based on billing records, which has inherent limitations. Another study concluded long term opioid use was more common among adults with ADHD who used stimulants (16.5%), than among those with ADHD who did not use stimulants (13.0%).[11]

In an effort to monitor and improve patient safety, the Oregon Health Authority (OHA) has collected data surrounding deaths related to substance abuse for the past 2 decades. As shown in **Figure 1**, the overdose death rates in adults between 45 and 64 years old caused by methamphetamine and psychostimulants is rising in Oregon. Data reported by the OHA does not differentiate between deaths caused by illicit methamphetamine, versus prescription stimulants in this graph. Stimulant prescribing in Oregon is also rising, but at a slow rate, while benzodiazepine and opioid prescribing is trending downward (**Figure 2**).

Figure 1: Overdose Deaths by Age

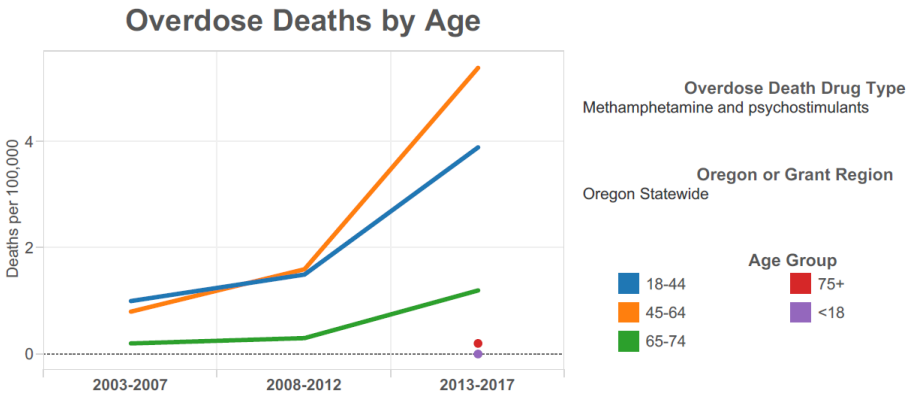
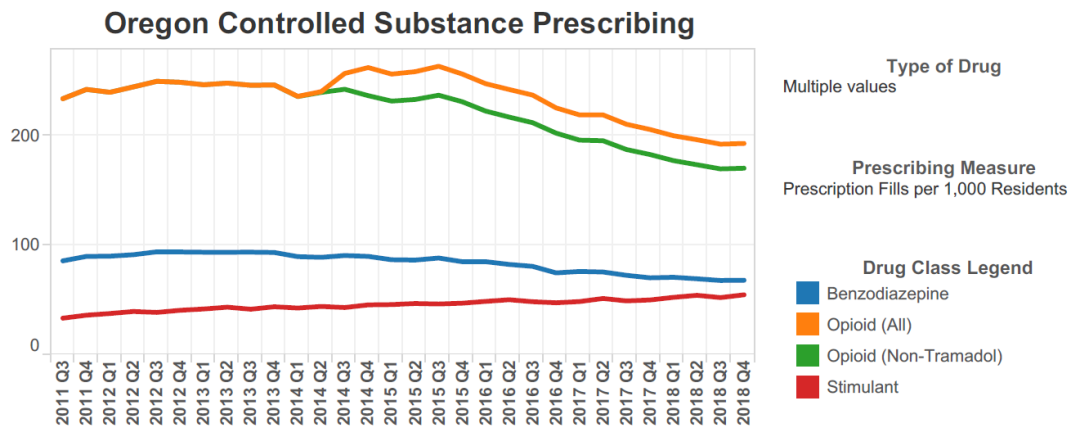


Figure 2: Oregon Controlled Substance Prescribing



In 2016, a drug utilization review of ADHD medications in Oregon Health Plan Fee-For-Service (FFS) patients showed an increase in use of ADHD medications in adults age 18 years or older from October 2014 through September 2015 (45%) compared to the year prior (28%). The exact reason for the increase in utilization for adults was unknown, but the finding was consistent with published literature showing an increase in ADHD simulant utilization in adults in the United States, from 10 million stimulant prescriptions dispensed in 1993, to 50 million in 2011, and 58 million in 2014.[12] Additionally, one third of the patients had a history of substance or alcohol abuse/dependence and over half of patients had a contraindication or precaution to use of these medications. There was no trend in increasing ED visits and/or hospitalizations. Based on these results, the P and T committee recommended to continue evaluating trends of ADHD medication utilization in adults.[13]

The purpose of this review it to evaluate the current prescribing patterns and utilization of ADHD medications in adults in the Oregon FFS population. Based on recent literature and the concern for increasing overdose deaths by stimulants, the review will also evaluate stimulant and non-stimulant use in patients with existing substance use disorder, prevalence of concurrent opioid use, and incidence of hospitalizations due to overdose.

Methods:

In order to illustrate trends over time, FFS ADHD pharmacy claims for adults (18 years or older) are graphed in **Figure 3** from 2014 through 2018 (adjusted to PMPM x 1000). **Figure 4** considers the same monthly utilization but is restricted to those patients with a diagnosis of substance or alcohol abuse/dependence in the year prior (using ICD codes from **Table A2**).

For a more detailed look at recent adult ADHD utilization, a cohort of new start patients was selected by the presence of a paid FFS pharmacy claim for any ADHD drug in **Table A1** from 1/1/2016 through 05/31/2018. The first FFS ADHD paid claim per patient during the study period was designated the index event (IE), and patients were excluded if they had any ADHD claim in the 90 days prior to the IE (FFS or CCO), so that duplicate patients would not be included. Patients were excluded if they were under the age of 18 at the time of the IE, or if they had Medicare Part D coverage as indicated by benefit packages of BMM, BMD, MND or MED. Patients were also excluded if they had less than 75% days of combined FFS or coordinated care organization eligibility from 11 months prior to

the index month to 3 months after the index month (for a total of 15 months) to ensure the most complete data possible. Finally, patients were excluded if they had a diagnosis of narcolepsy or sleep disorder in the year prior to the IE using ICD 9 and 10 codes from **Table A3.**

Baseline characteristics of age, gender, and ethnicity were assessed at the IE, and patients were also categorized by prescriber type and index drug (**Table 1**). Additionally, patients with concurrent use of stimulants and opioids, defined as use of opioid for >90 days with allowance for 1 week gap between refills were identified. Patients with a paid FFS or encounter claim with an ICD 9 or 10 diagnosis code for each of the diagnostic groups from **Table A2** were flagged in the year prior to the IE. Patients are categorized in the following mutually exclusive groups: 1) FDA labeled and funded, 2) FDA labeled and unfunded, 3) non-FDA labeled, and 4) none of the above (**Table 2**). Prevalence of hospitalizations and ED visits, both all-cause and related to overdose, were evaluated in the 90 days after the IE (**Table 4**).

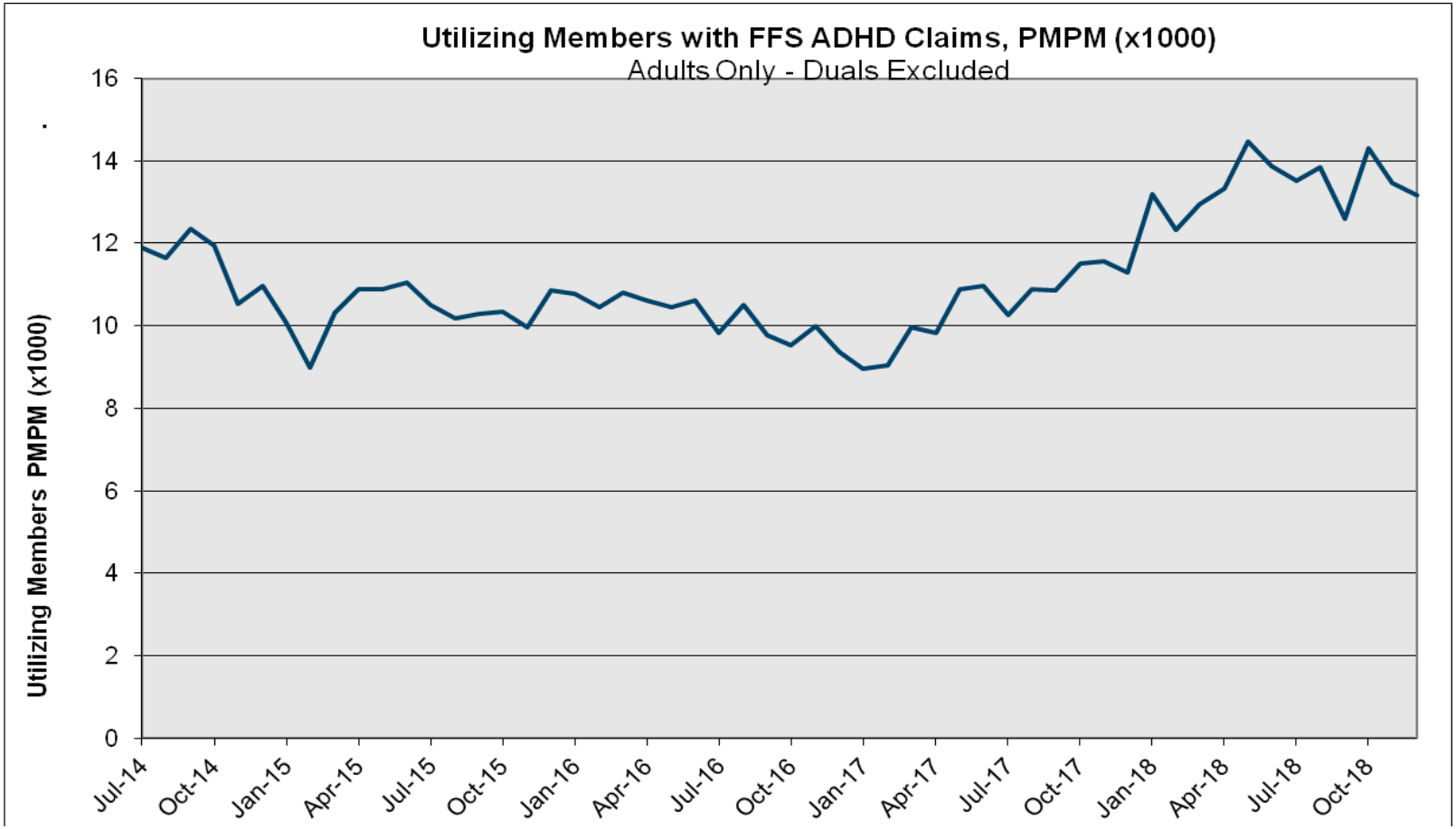
To gauge stimulant dose titration over time, a subgroup of the study cohort was selected based on the requirement they maintain therapy on the IE drug for six continuous months with no more than a 7 day gap in therapy between subsequent claims. From this group, the average daily dose of ADHD medication was compared at the IE and at 6 months after the IE, by index drug **(Table 5**).

Results:

ADHD Medication Utilization

Figure 3 illustrates trends of FFS ADHD pharmacy claims for adults from 2014 to 2018, adjusted to PMPM x 1000. There appears to be a trend upward since 2017.

Figure 3: ADHD Medication Utilization from 2012 to 2018 in Oregon Health Plan Fee-For-Service Population



Demographics of Claims Data

Patient demographics are included in **Table 1.** There were a total of 3,200 paid index events from January 2016 to May 2018. The previous DUE identified only 1,038 paid claims in adults in a one year time period. Most patients were between 25 and 54 years of age. There were 2,088 claims (65.3%) for atomoxetine, and majority of prescriptions were prescribed by physicians (43.2%) and advanced practice nurses (38.2%). Only a small portion of patients (0.9%) were found to be using ADHD medications concurrently with opioids for >90 days.

Table 1: Patient Demographics: Adults with FFS Pharmacy Claim for ADHD drug from January 2016-May 2018

	Index Event Paid Claim N=3,200	
Mean age (range)	34.8	(18-64)
18-24	592	18.5%
25-34	1,173	36.7%
35-54	1,226	38.3%
55-64	209	6.5%
65+	0	0.0%
Female	1,877	58.7%
Race		
White	1,794	56.1%
Other	190	5.9%
Unknown	1,216	38.0%
Patient Count by Index Drug		
armodafinil	46	1.4%
atomoxetine HCl	2,088	65.3%
dexmethylphenidate HCl	7	0.2%
dextroamphetamine sulfate	12	0.4%
dextroamphetamine/amphetamine	520	16.3%
lisdexamfetamine dimesylate	105	3.3%
methylphenidate	2	0.1%
methylphenidate HCl	232	7.3%
modafinil	188	5.9%
Index Drug PDL Status		
PDL = Preferred	2,810	87.8%
PDL = Voluntary Non-preferred	234	7.3%
PDL = Non-preferred	156	4.9%
Index Claim Prescriber Type	(Not mutually-exclusive)	
Physician	1,381	43.2%
Advance Practice Nurse	1,223	38.2%

MH Provider	1,091	34.1%
Physician Assistants	249	7.8%
Adv Comp Health Care	43	1.3%
Concurrent use of opioid for >=90 days	28	0.9%

Associated Diagnoses

Forty-two percent of patients had an FDA labeled and funded indication (ADD/ADHD, binge eating disorder, narcolepsy) for receiving ADHD medications (**Table 2**). This is slightly lower than what was seen in the previous DUE (53%). There was low overall use for exogenous obesity, which is an unfunded condition. Claims for ADHD medications associated with off-label conditions were not significant, and the majority of those claims were for major depressive disorder. Most notably, 36% of patients 18 years of age or older were lacking a diagnosis for the use of ADHD medications. Additionally, 36% of patients had a diagnosis of substance or alcohol abuse or dependence (**Table 3**). **Table 3** also shows that of the 2,088 patients prescribed atomoxetine, 45.5% had concomitant substance use disorder.

Table 2 - Associated Diagnoses in Year Prior to Index Event

Mutually-Exclusive categories

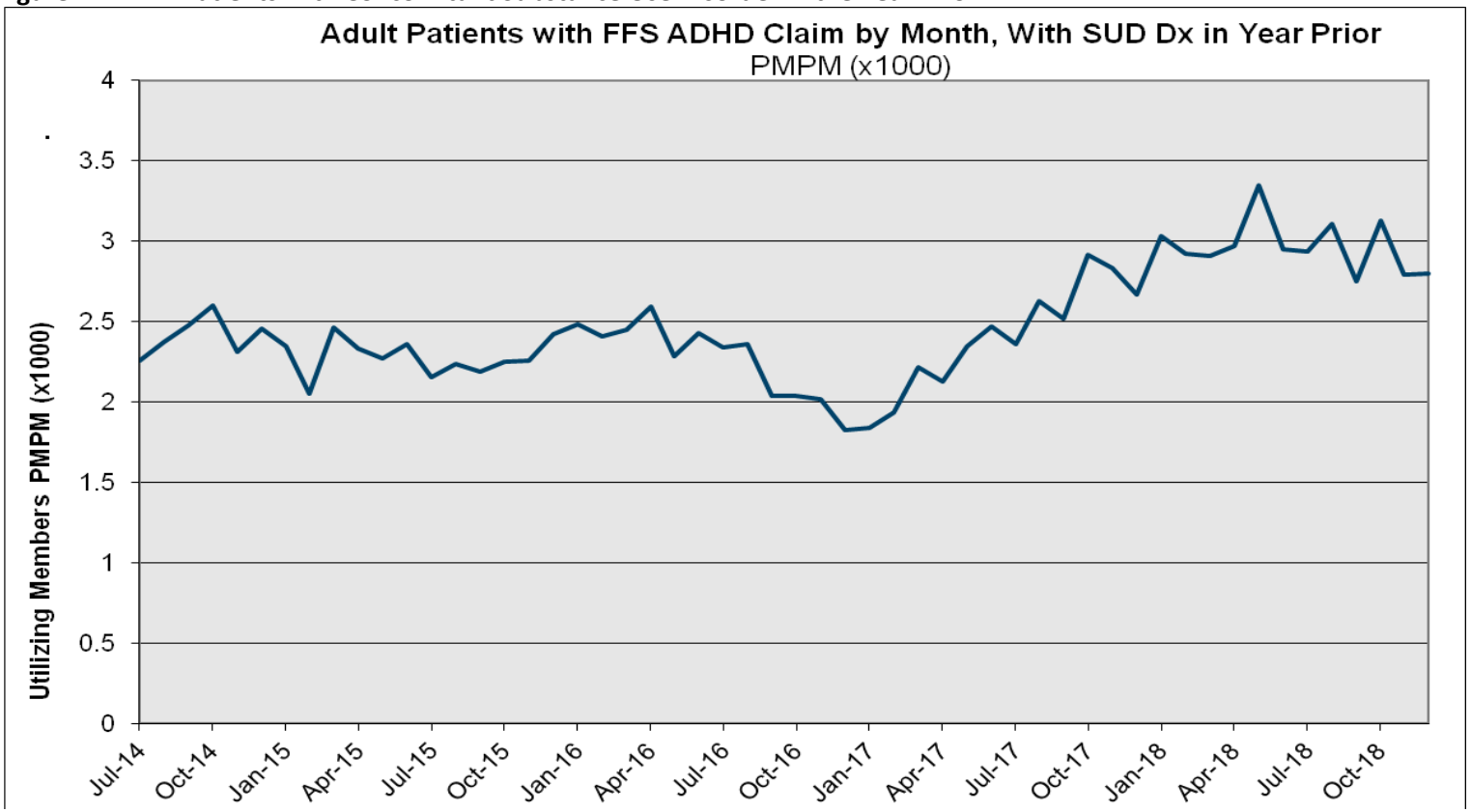
N=	3,200	%
FDA Labeled and Funded	1,333	41.7%
ADD/ADHD	1,326	41.4%
Binge Eating Disorder	19	0.6%
Narcolepsy - symptomatic management	0	0.0%
Unfunded, FDA Labeled	146	4.6%
Exogeneous obesity	146	4.6%
Off-Label Indications	562	17.6%
Major Depressive Disorder	494	15.4%
Chronic Fatigue	100	3.1%
Nocturnal enuresis	2	0.1%
None of the Above	1,159	36.2%

Table 3 - Contraindications in Year Prior to Index Event

	All		Patients with Atomoxetine IE	
N=	3,200	%	2,088	%
Substance or Alcohol Abuse/Dependence	1,138	35.6%	951	45.5%

Figure 4 assesses trends of utilization of ADHD medications in adults with concomitant substance use disorder. Trends in patients with substance use disorders appear consistent with trends in the overall population of patient's prescribed ADHD therapy.

Figure 4: ADHD Patients with Concomitant Substance Use Disorder in the Year Prior



ED/Hospitalizations

Of the patients receiving ADHD medications, **Table 4** highlights those with hospitalizations/ED visits for any cause, and hospitalizations/ED visits due to overdose of drug or alcohol. Less than 1% of patients using ADHD medications were hospitalized or visited the ED for drug (including CNS stimulants) or alcohol overdose.

Table 4 - ED/Hospitalizations within 90 Days of Index Event

N=	3,200	
All Cause ED/Hospitalizations	668	20.9%
ED/Hospitalizations due to overdose	25	0.8%

Dose Titration

Table 5 highlights dosage changes in patients with the same stimulant over 6 months. All ADHD medications were used appropriately and within the maximum dosage limits with the exception of armodafinil which has a max dosage of 250mg once daily. The most drastic increase in dosage was also for armodafinil, with an 88% increase in dosage after 6 months of use. The average starting dose was 200mg per day, and average dose 6 months after was 375mg per day.

Table 5 - Average Dose per Day at Index and 6 Months After Index
For patients with 6 months sustained therapy on same HSN as index.

N = 244	Max Dose per day (mg)	Index Claim Avg Dose per Day (mg)	Claim Six Months After Avg Dose per Day (mg)	% Change
armodafinil (TABLET)	250	200	375	87.5%
atomoxetine HCl (CAPSULE)	100	41	64	56.1%
dexmethylphenidate HCl (CPBP 50-50)	30-50	40	40	0.0%
dextroamphetamine sulfate (CAPSULE ER)	40-60	10	9	-13.3%
dextroamphetamine/amphetamine (CAP ER 24H)	50	21	28	29.1%
dextroamphetamine/amphetamine (TABLET)	50	29	35	21.1%
lisdexamfetamine dimesylate (CAPSULE)	70	39	49	25.6%
methylphenidate HCl (TAB ER 24)	60	49	47	-4.5%
methylphenidate HCl (TABLET ER)	60	40	40	0.0%
methylphenidate HCl (TABLET)	60	28	36	29.4%
modafinil (TABLET)	200	161	200	24.1%

Discussion:

The results of this DUE are consistent with recent literature, showing an increase of ADHD diagnosis in adults.[10] Based on the results in **Figure 3**, utilization of ADHD medications in adults has fluctuated, but ultimately increased from 11.9 to 13.15 PMPM x 1000 between 7/1/2014 and 12/1/2018. A significant portion of patients were receiving a stimulant medication without a relevant diagnosis reported in claims (36.2%). The proportion of patients has increased since 2015 when a prior evaluation in a similar population found that 26% of adults did not have a relevant diagnosis.[13] Current NICE guideline for the treatment and diagnosis of adult ADHD recommends that adult patients presenting with ADHD symptoms, with or without a childhood diagnosis, be referred for assessment by a mental health specialist for proper diagnosis of ADHD.[4]

Although it appears from our data that the most frequently prescribed ADHD medication in adults was atomoxetine (65%), this result may be exaggerated, since atomoxetine is a carved out medication. Therefore the total population (denominator) includes the entire Medicaid population, including the CCOs, and is much larger (approximately 1 million members) than the FFS population alone (approximately 100,000 total members). Nonetheless, first line therapy recommendations for adult ADHD are lisdexamfetamine or methylphenidate.[4] For unresponsive or intolerance to methylphenidate or potential of misuse/abuse, atomoxetine should be considered due to its unique mechanism of action. After atomoxetine, controlled-release formulations should be used due to less likelihood of abuse.[15]

It is also interesting to note that 36% of patients who were prescribed an ADHD medication had a diagnosis of substance or alcohol abuse disorder. This number is similar to data reported in 2016, in which 33% of adult patients also had a history of substance abuse.[13] Additionally, between 2014 and 2018, there has been a slight increase in ADHD claims in patients with substance use disorder compared to the year prior. Stimulants and controlled-substance medications have a high abuse potential, and therefore it would be assumed that use of these agents should be cautioned in patients with known substance abuse and a higher baseline chance of abuse. However, research studies do not support the claim that stimulant treatments add to the risk of substance abuse in the patients with ADHD.[14] The national comorbidity survey replication data showed 10-24% of adults with substance use disorder had ADHD.[15-17] However, the literature consistently demonstrates that adults with ADHD are more likely to have comorbidities than adults without ADHD, including anxiety, bipolar disorder, depression, and drug or alcohol abuse.[4,13,16] It is hypothesized that there is a neurobiological link between ADHD and substance use disorder due to evidence of structural brain abnormalities in individuals with ADHD.[18] This illustrates the importance of patients having appropriate diagnoses for these medications, especially adults, and having the medications prescribed by a mental health specialist.

Based on the average dose per day at upon initial prescribing and 6 months afterwards, all medications had appropriate dose increases within maximum dosage limits with the exception of armodafinil. The armodafinil dose seen after six months of use was 350mg, which exceeds the maximum recommended dose of 150 to 250mg per day for narcolepsy, obstructive sleep apnea and shift-work disorder.[19] Stimulants are found to have individual variability for dose response, which may be affected by slow/fast metabolizers.[20] In treatment of adult patients with ADHD, titration with discussion of response to drug as well as side effects is important to consider.[21]

Data collected by the OHA demonstrates an increase in stimulant and non-prescription methamphetamine overdose and related deaths in Oregon in the past several years. This was not validated by an assessment of claims for ED/hospitalizations due to drug overdose. Emergency department visits and hospitalization overall for any diagnosis in patients using ADHD medications was also relatively low. In the previous analysis of Medicaid data completed in 2016, the ED/hospitalization results within 90 days of ADHD medication use were also shown to be low, however hospitalizations due to drug overdose were not measured.[13] This leads to the conclusion that the data collected by OHA showing an increase in overdose related death is most likely due to non-prescription methamphetamine use, and not prescribed stimulants.

Limitations:

All of the data collected and analyzed was claims data, which limits the ability to directly connect a patient's diagnosis with the medications being prescribed. Claims data only allows researchers to make associations and assumptions about why patients are taking certain medications of interest, especially if patients do not have a diagnosis code on file. Data regarding provider types was collected using specialty provider codes, in attempt to compare and contrast prescriptions coming from recognized mental health providers as opposed to non-mental health specialists. However, these codes may not reliably identify all recognized mental health specialties, and therefore made it difficult to infer how many prescriptions were from mental health specialists. Only claims data was assessed for index events. The data could be analyzed more in depth if recurrent patients and utilization was included in the report.

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Appendix 1:

Table A1: Codes identifying ADHD drugs in fee-for-service or managed care pharmacy or professional claims

GSN	Generic	Strength	mg per Unit	Formulation	ER	PDL	Max Daily Units
004999	DEXTROAMPHETAMINE/AMPHETAMINE	5 mg	5	TABLET	0	1	12
005000	DEXTROAMPHETAMINE/AMPHETAMINE	10 mg	10	TABLET	0	1	6
005001	DEXTROAMPHETAMINE/AMPHETAMINE	20 mg	20	TABLET	0	1	3
034359	DEXTROAMPHETAMINE/AMPHETAMINE	30 mg	30	TABLET	0	1	2
047131	DEXTROAMPHETAMINE/AMPHETAMINE	7.5 mg	7.5	TABLET	0	1	8
047132	DEXTROAMPHETAMINE/AMPHETAMINE	12.5 mg	12.5	TABLET	0	1	4.8
047133	DEXTROAMPHETAMINE/AMPHETAMINE	15 mg	15	TABLET	0	1	4
048701	DEXTROAMPHETAMINE/AMPHETAMINE	10 mg	10	CAP ER 24H	1	0	3
048702	DEXTROAMPHETAMINE/AMPHETAMINE	20 mg	20	CAP ER 24H	1	0	1.5
048703	DEXTROAMPHETAMINE/AMPHETAMINE	30 mg	30	CAP ER 24H	1	0	1
050428	DEXTROAMPHETAMINE/AMPHETAMINE	5 mg	5	CAP ER 24H	1	0	6
050429	DEXTROAMPHETAMINE/AMPHETAMINE	15 mg	15	CAP ER 24H	1	0	2
050430	DEXTROAMPHETAMINE/AMPHETAMINE	25 mg	25	CAP ER 24H	1	0	1.2
061443	METHYLPHENIDATE HCL	10 mg	10	CSBP 40-60	1	0	7.2
061444	METHYLPHENIDATE HCL	15 mg	15	CSBP 40-60	1	0	4.8
061445	METHYLPHENIDATE HCL	20 mg	20	CSBP 40-60	1	0	3.6
061446	METHYLPHENIDATE HCL	30 mg	30	CSBP 40-60	1	0	2.4
061447	METHYLPHENIDATE HCL	40 mg	40	CSBP 40-60	1	0	1.8
061448	METHYLPHENIDATE HCL	50 mg	50	CSBP 40-60	1	0	1.4
061449	METHYLPHENIDATE HCL	60 mg	60	CSBP 40-60	1	0	1.2
060615	METHYLPHENIDATE	10 mg /9 hr	10	PATCH TD24	1	1	3
060616	METHYLPHENIDATE	15 mg/ 9 hr	15	PATCH TD24	1	1	2
060617	METHYLPHENIDATE	20 mg/ 9 hr	20	PATCH TD24	1	1	1.5
060618	METHYLPHENIDATE	30 mg/ 9 hr	30	PATCH TD24	1	1	1
005009	DEXTROAMPHETAMINE SULFATE	10 mg	10	TABLET	0	0	4
005011	DEXTROAMPHETAMINE SULFATE	5 mg	5	TABLET	0	0	8
048982	DEXMETHYLPHENIDATE HCL	2.5 mg	2.5	TABLET	0	0	8
048983	DEXMETHYLPHENIDATE HCL	5 mg	5	TABLET	0	0	4

048984	DEXMETHYLPHENIDATE HCL	10 mg	10	TABLET	0	0	2
064090	DEXTROAMPHETAMINE SULFATE	5 mg/5 mL	1	SOLUTION	0	0	40
005005	DEXTROAMPHETAMINE SULFATE	10 mg	10	CAPSULE ER	1	0	6
005006	DEXTROAMPHETAMINE SULFATE	15 mg	15	CAPSULE ER	1	0	4
005007	DEXTROAMPHETAMINE SULFATE	5 mg	5	CAPSULE ER	1	0	12
075025	DEXTROAMPHETAMINE/AMPHETAMINE	2.5 mg/mL	2.5	SUS BP 24H	1	0	24
005002	AMPHETAMINE SULFATE	10 mg	10	TABLET	0	0	6
005003	AMPHETAMINE SULFATE	5 mg	5	TABLET	0	0	12
059190	DEXMETHYLPHENIDATE HCL	5 mg	5	CPBP 50-50	1	1	6 if <18 yo 8 if ≥18 yo
059191	DEXMETHYLPHENIDATE HCL	10 mg	10	CPBP 50-50	1	1	3 if <18 yo 4 if ≥18 yo
059192	DEXMETHYLPHENIDATE HCL	20 mg	20	CPBP 50-50	1	1	1.5 if <18 yo 2 if ≥18 yo
061317	DEXMETHYLPHENIDATE HCL	15 mg	15	CPBP 50-50	1	1	2 if <18 yo 2.7 if ≥18 yo
065909	DEXMETHYLPHENIDATE HCL	30 mg	30	CPBP 50-50	1	1	1 if <18 yo 1.3 if ≥18 yo
066611	DEXMETHYLPHENIDATE HCL	40 mg	40	CPBP 50-50	1	1	0.75 if <18 yo 1 if ≥18 yo
067692	DEXMETHYLPHENIDATE HCL	25 mg	25	CPBP 50-50	1	1	1.2 if <18 yo 1.6 if ≥18 yo
067693	DEXMETHYLPHENIDATE HCL	35 mg	35	CPBP 50-50	1	1	0.86 if <18 yo 1.1 if ≥18 yo
005014	METHAMPHETAMINE HCL	5 mg	5	TABLET	0	0	Not established
054676	METHYLPHENIDATE HCL	2.5 mg	2.5	TAB CHEW	0	0	24
054677	METHYLPHENIDATE HCL	5 mg	5	TAB CHEW	0	0	12
054678	METHYLPHENIDATE HCL	10 mg	10	TAB CHEW	0	0	6
054679	METHYLPHENIDATE HCL	5 mg/5 mL	1	SOLUTION	0	0	60
054680	METHYLPHENIDATE HCL	10 mg/5 mL	2	SOLUTION	0	0	30
004029	METHYLPHENIDATE HCL	20 mg	20	TABLET ER	1	0	3.6
044072	METHYLPHENIDATE HCL	10 mg	10	TABLET ER	1	0	7.2
045981	METHYLPHENIDATE HCL	18 mg	18	TAB ER 24	1	0	4

045982	METHYLPHENIDATE HCL	36 mg	36	TAB ER 24	1	0	2
047318	METHYLPHENIDATE HCL	54 mg	54	TAB ER 24	1	0	1.3
050172	METHYLPHENIDATE HCL	27 mg	27	TAB ER 24	1	0	2.7
004026	METHYLPHENIDATE HCL	10 mg	10	TABLET	0	1	10
004027	METHYLPHENIDATE HCL	20 mg	20	TABLET	0	1	3
004028	METHYLPHENIDATE HCL	5 mg	5	TABLET	0	1	12
053056	METHYLPHENIDATE HCL	10 mg	10	CPBP 30-70	1	0	7.2
053057	METHYLPHENIDATE HCL	20 mg	20	CPBP 30-70	1	0	3.6
053058	METHYLPHENIDATE HCL	30 mg	30	CPBP 30-70	1	0	2.4
060545	METHYLPHENIDATE HCL	40 mg	40	CPBP 30-70	1	0	1.8
060546	METHYLPHENIDATE HCL	50 mg	50	CPBP 30-70	1	0	1.4
060547	METHYLPHENIDATE HCL	60 mg	60	CPBP 30-70	1	0	1.2
075263	METHYLPHENIDATE HCL	20 mg	20	TAB CBP24H	1	0	3.6
075264	METHYLPHENIDATE HCL	30 mg	30	TAB CBP24H	1	0	2.4
075265	METHYLPHENIDATE HCL	40 mg	40	TAB CBP24H	1	0	1.8
070374	METHYLPHENIDATE HCL	5 mg/mL (25 mg/5 mL)	5	SU ER RC24	1	0	14.4
053059	METHYLPHENIDATE HCL	20 mg	20	CPBP 50-50	1	0	3.6
053060	METHYLPHENIDATE HCL	30 mg	30	CPBP 50-50	1	0	2.4
053061	METHYLPHENIDATE HCL	40 mg	40	CPBP 50-50	1	0	1.8
053974	METHYLPHENIDATE HCL	10 mg	10	CPBP 50-50	1	0	7.2
072092	METHYLPHENIDATE HCL	60 mg	60	CPBP 50-50	1	0	1.2
051489	ATOMOXETINE HCL	10 mg	10	CAPSULE	0	1	10
051490	ATOMOXETINE HCL	18 mg	18	CAPSULE	0	1	5.6
051491	ATOMOXETINE HCL	25 mg	25	CAPSULE	0	1	4
051492	ATOMOXETINE HCL	40 mg	40	CAPSULE	0	1	2.5
051493	ATOMOXETINE HCL	60 mg	60	CAPSULE	0	1	1.7
060390	ATOMOXETINE HCL	80 mg	80	CAPSULE	0	1	1.25
060391	ATOMOXETINE HCL	100 mg	100	CAPSULE	0	1	1
062283	LISDEXAMFETAMINE DIMESYLATE	30 mg	30	CAPSULE	0	1	2.3
062284	LISDEXAMFETAMINE DIMESYLATE	50 mg	50	CAPSULE	0	1	1.4
062285	LISDEXAMFETAMINE DIMESYLATE	70 mg	70	CAPSULE	0	1	1
063645	LISDEXAMFETAMINE DIMESYLATE	20 mg	20	CAPSULE	0	1	3.5

063646	LISDEXAMFETAMINE DIMESYLATE	40 mg	40	CAPSULE	0	1	1.75
063647	LISDEXAMFETAMINE DIMESYLATE	60 mg	60	CAPSULE	0	1	1.2
073292	LISDEXAMFETAMINE DIMESYLATE	10 mg	10	CAPSULE	0	1	7
005009	DEXTROAMPHETAMINE SULFATE	10 mg	10	TABLET	0	0	4
005010	DEXTROAMPHETAMINE SULFATE	15 mg	15	TABLET	0	0	2.7
005011	DEXTROAMPHETAMINE SULFATE	5 mg	5	TABLET	0	0	8
071048	DEXTROAMPHETAMINE SULFATE	2.5 mg	2.5	TABLET	0	0	16
071049	DEXTROAMPHETAMINE SULFATE	7.5 mg	7.5	TABLET	0	0	5.3
072313	DEXTROAMPHETAMINE SULFATE	20 mg	20	TABLET	0	0	2
072314	DEXTROAMPHETAMINE SULFATE	30 mg	30	TABLET	0	0	1.3
025848	MODAFINIL	100 mg	100	TABLET	0	0	2
041478	MODAFINIL	200 mg	200	TABLET	0	0	1
062819	ARMODAFINIL	150 mg	150	TABLET	0	0	1
062820	ARMODAFINIL	50 mg	50	TABLET	0	0	5
062821	ARMODAFINIL	250 mg	250	TABLET	0	0	1
072017	ARMODAFINIL	200 mg	200	TABLET	0	0	1

Abbreviations: PDL = preferred drug list

HSN = hierarchical ingredient code list (HICL) sequence number as reported by First DataBank™

Table A2: Indications and Contraindications/Precautions for ADHD Medications

**Approved for lisdexamfetamine only*

ICD-9	Diagnosis	ICD-10	Diagnosis
FDA Labeled Indications			
314.00- 314.9	Attention-deficit hyperactivity disorder (ADHD)/ Attention deficit disorder (ADD)	F90.9 F90.1 F90.2 F90.8 F90.9	Attention-deficit hyperactivity disorder (ADHD)/ Attention deficit disorder (ADD) Attention-deficit hyperactivity disorders Attention-deficit hyperactivity disorder, predominantly inattentive type Attention-deficit hyperactivity disorder, predominantly hyperactive type Attention-deficit hyperactivity disorder, combined type Attention-deficit hyperactivity disorder, other type Attention-deficit hyperactivity disorder, unspecified type
347.10- 347.11	Narcolepsy - symptomatic management	Not included	

307.5	Binge Eating Disorder*	F50.81, F50.02	Binge Eating Disorder*, binge eating/purging type
Unfunded FDA Labeled Indications			
278.01	Exogenous obesity	E66.01	Morbid (severe) obesity due to excess calories/Exogenous obesity
Unlabeled Indications			
296.3, 296.20-296.22, 296.25-296.26, 296.90-296.99, 298.0, 311, 625.4	Major depressive disorder (MDD) recurrent, unspecified	F32.0 F32.1 F32.2 F32.3 F32.4 F32.5 F33.0 F33.1 F33.2 F33.3 F33.4 F33.40 F33.41 F33.42	Major depressive disorder, single episode Major depressive disorder, single episode, mild Major depressive disorder, single episode, moderate Major depressive disorder, single episode, severe without psychotic features Major depressive disorder, single episode, severe with psychotic features Major depressive disorder, single episode, severe with psychotic features Major depressive disorder, single episode, in partial remission Major depressive disorder, single episode, in full remission Major depressive disorder (MDD) recurrent, unspecified Major depressive disorder, recurrent, mild Major depressive disorder, recurrent, moderate Major depressive disorder, recurrent, severe without psychotic features Major depressive disorder, recurrent, severe with psychotic features Major depressive disorder, recurrent, in remission Major depressive disorder, recurrent, in remission, unspecified Major depressive disorder, recurrent, in partial remission Major depressive disorder, recurrent, in full remission
788.36	Nocturnal enuresis	N39.44	Nocturnal enuresis
Chronic Fatigue			
780.71-780.72, 780.79, 140.xx, 209.xx	Fatigue in adult cancer survivors	R53.0	Fatigue in adult cancer survivors
340.xx	Multiple Sclerosis-related fatigue		
780.71	Chronic Fatigue Syndrome	R53.82	Chronic fatigue, **unspecified**
None of the Above			
Contraindications or precautions			
Substance or Alcohol Abuse/Dependence			
305.00-305.03 291.81 291.0	Alcohol dependence syndrome Alcohol Abuse Alcohol withdrawal delirium Alcohol-induced persisting amnestic disorder	R780 F10.23 F10.2 F10.239	Finding of alcohol in blood Alcohol dependence and withdrawal Alcohol dependence Dependence on alcohol with withdrawal

291.1	Alcohol-induced persisting dementia	F10	Alcohol related disorders
291.2	Alcohol-induced psychotic disorder with	F1010	Alcohol abuse, uncomplicated
291.3	hallucinations	F10120	Alcohol abuse with intoxication, uncomplicated
291.4	Idiosyncratic alcohol intoxication	F10121	Alcohol abuse with intoxication delirium
291.5	Alcohol-induced psychotic disorder with delusions	F10129	Alcohol abuse with intoxication, unspecified
291.8	Other specified alcohol-induced mental disorders	F1014	Alcohol abuse with alcohol-induced mood disorder
291.82	Alcohol withdrawal	F10150	Alcohol abuse with alcohol-induce psychotic disorder with delusions
291.89	Alcohol-induced sleep disorders	F10151	Alcohol abuse with alcohol-induce psychotic disorder with hallucinations
291.9	Other alcohol-induced disorders	F10159	Alcohol abuse with alcohol-induced psychotic disorder, unspecified
303.00–	Unspecified alcohol-induced mental disorders	F10180	Alcohol abuse with alcohol-induced anxiety disorder
303.03	Acute alcohol intoxication	F10181	Alcohol abuse with alcohol-induced sexual dysfunction
303.90–	Other and unspecified alcohol dependence	F10182	Alcohol abuse with alcohol-induced sleep disorder
303.93		F10188	Alcohol abuse with other alcohol-induced disorder
		F1019	Alcohol abuse with unspecified alcohol-induced disorder
		F1020	Alcohol dependence, uncomplicated
		F1021	Alcohol dependence, in remission
		F10220	Alcohol dependence with intoxication, uncomplicated
		F10221	Alcohol dependence with intoxication delirium
		F10229	Alcohol dependence with intoxication, unspecified
		F10230	Alcohol dependence with withdrawal, uncomplicated
		F10231	Alcohol dependence with withdrawal delirium
		F10232	Alcohol dependence with withdrawal with perceptual disturbance
		F10239	Alcohol dependence with withdrawal, unspecified
		F1024	Alcohol dependence with alcohol-induced mood disorder
		F10250	Alcohol dependence with alcohol-induce psychotic disorder with delusions
		F10251	Alcohol dependence with alcohol-induce psychotic disorder with hallucinations
		F10259	Alcohol dependence with alcohol-induce psychotic disorder, unspecified
		F10280	Alcohol dependence with alcohol-induced anxiety disorder
		F10281	Alcohol dependence with alcohol-induced sexual dysfunction
		F10282	Alcohol dependence with alcohol-induced sleep disorder
		F10288	Alcohol dependence with other alcohol-induced disorder
		F1029	Alcohol dependence with unspecified alcohol-induced disorder
		F10920	Alcohol use, unspecified with intoxication, uncomplicated
		F10921	Alcohol use, unspecified with intoxication delirium
		F10929	Alcohol use, unspecified with intoxication, unspecified
		F1094	Alcohol use, unspecified with alcohol-induced mood disorder
		F10950	Alcohol use, unspecified with alcohol-induce psychotic disorder with delusions
		F10951	Alcohol use, unspecified with alcohol-induce psychotic disorder with
		F10959	hallucinations

		F10980	Alcohol use, unspecified with alcohol-induced psychotic disorder, unspecified
		F10981	Alcohol use, unspecified with alcohol-induced anxiety disorder
		F10982	Alcohol use, unspecified with alcohol-induced sexual dysfunction
		F10288	Alcohol use, unspecified with alcohol-induced sleep disorder
		F1029	Alcohol use, unspecified with other alcohol-induced disorder
		F10920	Alcohol use, unspecified with unspecified alcohol-induced disorder
		F10921	
		F10929	
		F1094	
		F10950	
		F10951	
		F10959	
		F10980	
		F10981	
		F10982	
		F10988	
		F1099	
304.00– 304.03 304.70– 304.73 305.50– 305.53 304.80– 304.83 304.90– 304.93 Other, mixed or unspecified drug abuse V654.2	Opioid type dependence Combinations of opioids with any other Nondependent opioid abuse Combinations excluding opioids Unspecified drug dependence Other, mixed or unspecified drug abuse Counseling, substance use	R781 F1110 F11120 F11121 F11122 F11129 F1114 F11150 F11151 F11159 F11181 F11182 F11188 F1119	Finding of opiate drug in blood Opioid abuse, uncomplicated Opioid abuse with intoxication, uncomplicated Opioid abuse with intoxication delirium Opioid abuse with intoxication with perceptual disturbance Opioid abuse with intoxication, unspecified Opioid abuse with opioid-induced mood disorder Opioid abuse with opioid-induced psychotic disorder with delusions Opioid abuse with opioid-induced psychotic disorder with hallucinations Opioid abuse with opioid-induced psychotic disorder, unspecified Opioid abuse with opioid-induced sexual dysfunction Opioid abuse with opioid-induced sleep disorder Opioid abuse with other opioid-induced disorder Opioid abuse with unspecified opioid-induced disorder
304.30– 304.33 305.20– 305.23	Cannabis abuse Cannabis dependence Nondependent cannabis abuse	F12.9 F12.92 F12.921 F12.922 F12.929 F12.95 F12.951	Cannabis use, unspecified Cannabis use, unspecified with intoxication Cannabis use, unspecified with intoxication delirium Cannabis use, unspecified with intoxication with perceptual disturbance Cannabis use, unspecified with intoxication, unspecified Cannabis use, unspecified with psychotic disorder Cannabis use, unspecified with psychotic disorder with hallucinations

		F12.959 F12.98 F12.980 F12.988 F12.99	Cannabis use, unspecified with psychotic disorder, unspecified Cannabis use, unspecified with other cannabis-induced disorder Cannabis use, unspecified with anxiety disorder
303.90- 303.93	Other and unspecific alcohol dependence	F1120 F1121 F11220 F11221 F11222 F11229 F1123 F1124 F11250 F11251 F11259 F11281 F11282 F11288 F1129 F1190 F11920 F11921 F11922 F11929 F1193 F1194 F11950 F11951 F11959 F11981 F11988 F1199 F1210	Opioid dependence, uncomplicated Opioid dependence, in remission Opioid dependence with intoxication, uncomplicated Opioid dependence with intoxication delirium Opioid dependence with intoxication with perceptual disturbance Opioid dependence with intoxication, unspecified Opioid dependence with withdrawal Opioid dependence with opioid-induced mood disorder Opioid dependence with opioid-induced psychotic disorder with delusions Opioid dependence with opioid-induced psychotic disorder with hallucinations Opioid dependence with opioid-induced psychotic disorder, unspecified Opioid dependence with opioid-induced sexual dysfunction Opioid dependence with opioid-induced sleep disorder Opioid dependence with other opioid-induced disorder Opioid dependence with unspecified opioid-induced disorder Opioid use, unspecified, uncomplicated Opioid use, unspecified with intoxication, uncomplicated Opioid use, unspecified with intoxication delirium Opioid use, unspecified with intoxication with perceptual disturbance Opioid use, unspecified with intoxication, unspecified Opioid use, unspecified with withdrawal Opioid use, unspecified with opioid-induced mood disorder Opioid use, unspecified with opioid-induced psychotic disorder with delusions Opioid use, unspecified with opioid-induced psychotic disorder with Hallucinations Opioid use, unspecified with opioid-induced psychotic disorder, unspecified Opioid use, unspecified with opioid-induced sexual dysfunction Opioid use, unspecified with opioid-induced sleep disorder Opioid use, unspecified with other opioid-induced disorder Opioid use, unspecified with unspecified opioid-induced disorder
304.10– 304.13 305.40– 305.43	Sedatives, hypnotics, or anxiolytic dependence Nondependent sedative, hypnotic, or anxiolytic abuse	F1310 F13120 F13121 F13129	Sedative, hypnotic or anxiolytic abuse, uncomplicated Sedative, hypnotic or anxiolytic abuse with intoxication, uncomplicated Sedative, hypnotic or anxiolytic abuse with intoxication delirium Sedative, hypnotic or anxiolytic abuse with intoxication, unspecified

		F1314	Sedative, hypnotic or anxiolytic abuse with sedative, hypnotic or anxiolytic
		F13150	induced mood disorder
		F13151	Sedative, hypnotic or anxiolytic abuse with sedative, hypnotic or anxiolytic
		F13159	induced psychotic disorder with delusions
		F13180	Sedative, hypnotic or anxiolytic abuse with sedative, hypnotic or anxiolytic
		F13181	induced
		F13182	psychotic disorder with hallucinations
		F13188	Sedative, hypnotic or anxiolytic abuse with sedative, hypnotic or anxiolytic
		F1319	induced psychotic disorder, unspecified
		F1320	Sedative, hypnotic or anxiolytic abuse with sedative, hypnotic or anxiolytic
		F1321	induced anxiety disorder
		F13220	Sedative, hypnotic or anxiolytic abuse with sedative, hypnotic or anxiolytic
		F13221	induced
		F13229	sexual dysfunction
		F13230	Sedative, hypnotic or anxiolytic abuse with sedative, hypnotic or anxiolytic
		F13231	induced sleep disorder
		F13232	Sedative, hypnotic or anxiolytic abuse with other sedative, hypnotic or
		F13239	anxiolytic-induced disorder
		F1324	Sedative, hypnotic or anxiolytic abuse with unspecified sedative, hypnotic or
		F13250	anxiolytic-induced disorder
		F13251	Sedative, hypnotic or anxiolytic dependence, uncomplicated
		F13259	Sedative, hypnotic or anxiolytic dependence, in remission
		F13280	Sedative, hypnotic or anxiolytic dependence with intoxication, uncomplicated
		F13281	Sedative, hypnotic or anxiolytic dependence with intoxication delirium
		F13282	Sedative, hypnotic or anxiolytic dependence with intoxication, unspecified
		F13288	Sedative, hypnotic or anxiolytic dependence with withdrawal, uncomplicated
		F1329	Sedative, hypnotic or anxiolytic dependence with withdrawal delirium
		F1390	Sedative, hypnotic or anxiolytic dependence with withdrawal with perceptual
		F13920	Disturbance
		F13921	Sedative, hypnotic or anxiolytic dependence with withdrawal, unspecified
		F13929	Sedative, hypnotic or anxiolytic dependence with sedative, hypnotic or
		F13930	anxiolytic-induced mood disorder
		F13931	Sedative, hypnotic or anxiolytic dependence with sedative, hypnotic or
		F13932	anxiolytic-induced psychotic disorder with delusions
		F13939	Sedative, hypnotic or anxiolytic dependence with sedative, hypnotic or
		F1394	anxiolytic-induced psychotic disorder with hallucinations
		F13950	Sedative, hypnotic or anxiolytic dependence with sedative, hypnotic or
		F13951	anxiolytic-induced psychotic disorder, unspecified
		F13959	Sedative, hypnotic or anxiolytic dependence with sedative, hypnotic or

		F13980 F13981 F13982 F13988 F1399	anxiolytic-induced anxiety disorder Sedative, hypnotic or anxiolytic dependence with sedative, hypnotic or anxiolytic-induced sexual dysfunction Sedative, hypnotic or anxiolytic dependence with sedative, hypnotic or anxiolytic-induced sleep disorder Sedative, hypnotic or anxiolytic dependence with other sedative, hypnotic or anxiolytic-induced disorder Sedative, hypnotic or anxiolytic dependence with unspecified sedative, hypnotic or anxiolytic-induced disorder Sedative, hypnotic, or anxiolytic use, unspecified, uncomplicated Sedative, hypnotic, or anxiolytic use, unspecified with intoxication, Uncomplicated Sedative, hypnotic, or anxiolytic use, unspecified with intoxication delirium Sedative, hypnotic, or anxiolytic use, unspecified with intoxication, unspecified Sedative, hypnotic, or anxiolytic use, unspecified with withdrawal, uncomplicated Sedative, hypnotic, or anxiolytic use, unspecified with withdrawal delirium Sedative, hypnotic, or anxiolytic use, unspecified with withdrawal with perceptual disturbances Sedative, hypnotic, or anxiolytic use, unspecified with withdrawal, unspecified Sedative, hypnotic, or anxiolytic use, unspecified with sedative, hypnotic, or anxiolytic-induced mood disorder Sedative, hypnotic, or anxiolytic use, unspecified with sedative, hypnotic, or anxiolytic-induced psychotic disorder with delusions Sedative, hypnotic, or anxiolytic use, unspecified with sedative, hypnotic, or anxiolytic-induced psychotic disorder with hallucinations Sedative, hypnotic, or anxiolytic use, unspecified with sedative, hypnotic, or anxiolytic-induced psychotic disorder with, unspecified Sedative, hypnotic, or anxiolytic use, unspecified with sedative, hypnotic, or anxiolytic-induced anxiety disorder Sedative, hypnotic, or anxiolytic use, unspecified with sedative, hypnotic, or anxiolytic-induced sexual dysfunction Sedative, hypnotic or anxiolytic use, unspecified with sedative, hypnotic, or anxiolytic-induced sleep disorder Sedative, hypnotic or anxiolytic use, unspecified with other sedative, hypnotic, or anxiolytic-induced disorder Sedative, hypnotic or anxiolytic use, unspecified with unspecified sedative, hypnotic, or anxiolytic-induced disorder

		R782	Finding of cocaine in blood
		F1410	Cocaine abuse, uncomplicated
		F14120	Cocaine abuse with intoxication, uncomplicated
		F14121	Cocaine abuse with intoxication with delirium
		F14122	Cocaine abuse with intoxication with perceptual disturbance
		F14129	Cocaine abuse with intoxication, unspecified
		F1414	Cocaine abuse with cocaine-induced mood disorder
		F14150	Cocaine abuse with cocaine-induced psychotic disorder with delusions
		F14151	Cocaine abuse with cocaine-induced psychotic disorder with hallucinations
		F14159	Cocaine abuse with cocaine-induced psychotic disorder, unspecified
		F14180	Cocaine abuse with cocaine-induced anxiety disorder
		F14181	Cocaine abuse with cocaine-induced sexual dysfunction
		F14182	Cocaine abuse with cocaine-induced sleep disorder
		F14188	Cocaine abuse with other cocaine-induced disorder
		F1419	Cocaine abuse with unspecified cocaine-induced disorder
		F1420	Cocaine dependence, uncomplicated
		F1421	Cocaine dependence, in remission
304.20–		F14220	Cocaine dependence with intoxication, uncomplicated
304.23	Cocaine dependence	F14221	Cocaine dependence with intoxication delirium
305.60–	Nondependent cocaine abuse	F14222	Cocaine dependence with intoxication with perceptual disturbance
305.63		F14229	Cocaine dependence with intoxication, unspecified
		F1423	Cocaine dependence with withdrawal
		F1424	Cocaine dependence with cocaine-induced mood disorder
		F14250	Cocaine dependence with cocaine-induced psychotic disorder with delusions
		F14251	Cocaine dependence with cocaine-induced psychotic disorder with
		F14259	hallucinations
		F14280	Cocaine dependence with cocaine-induced psychotic disorder, unspecified
		F14281	Cocaine dependence with cocaine-induced anxiety disorder
		F14282	Cocaine dependence with cocaine-induced sexual dysfunction
		F14288	Cocaine dependence with cocaine-induced sleep disorder
		F1429	Cocaine dependence with other cocaine-induced disorder
		F1490	Cocaine dependence with unspecified cocaine-induced disorder
		F14920	Cocaine use, unspecified, uncomplicated
		F14921	Cocaine use, unspecified with intoxication, uncomplicated
		F14922	Cocaine use, unspecified with intoxication delirium
		F14929	Cocaine use, unspecified with intoxication with perceptual disturbance
		F1494	Cocaine use, unspecified with intoxication, unspecified
		F14950	Cocaine use, unspecified with cocaine-induced mood disorder
		F14951	

		F14959 F14980 F14981 F14982 F14988 F1499	Cocaine use, unspecified with cocaine-induced psychotic disorder with Delusions Cocaine use, unspecified with cocaine-induced psychotic disorder with hallucinations Cocaine use, unspecified with cocaine-induced psychotic disorder, unspecified Cocaine use, unspecified with cocaine-induced anxiety disorder Cocaine use, unspecified with cocaine-induced sexual dysfunction Cocaine use, unspecified with cocaine-induced sleep disorder Cocaine use, unspecified with other cocaine-induced disorder Cocaine use, unspecified with unspecified cocaine-induced disorder
304.40– 304.43 305.70– 305.73	Amphetamines dependence Nondependent amphetamine abuse	F1510 F15120 F15121 F15122 F15129 F1514 F15150 F15151 F15159 F15180 F15181 F15182 F15188 F1519 F1520 F1521 F15220 F15221 F15222 F15229 F1523 F1524 F15250 F15251 F15259 F15280 F15281 F15282 F15288	Other stimulant abuse, uncomplicated Other stimulant abuse with intoxication, uncomplicated Other stimulant abuse with intoxication delirium Other stimulant abuse with intoxication with perceptual disturbance Other stimulant abuse with intoxication, unspecified Other stimulant abuse with stimulant-induced mood disorder Other stimulant abuse with stimulant-induced psychotic disorder with delusions Other stimulant abuse with stimulant-induced psychotic disorder with hallucinations Other stimulant abuse with stimulant-induced psychotic disorder, unspecified Other stimulant abuse with stimulant-induced anxiety disorder Other stimulant abuse with stimulant-induced sexual dysfunction Other stimulant abuse with stimulant-induced sleep disorder Other stimulant abuse with other stimulant-induced disorder Other stimulant abuse with unspecified stimulant-induced disorder Other stimulant dependence, uncomplicated Other stimulant dependence, in remission Other stimulant dependence with intoxication, uncomplicated Other stimulant dependence with intoxication delirium Other stimulant dependence with intoxication with perceptual disturbance Other stimulant dependence with intoxication, unspecified Other stimulant dependence with withdrawal Other stimulant dependence with stimulant-induced mood disorder Other stimulant dependence with stimulant-induced psychotic disorder with delusions Other stimulant dependence with stimulant-induced psychotic disorder with hallucinations Other stimulant dependence with stimulant-induced psychotic disorder, Unspecified

		F1529	Other stimulant dependence with stimulant-induced anxiety disorder
		F1590	Other stimulant dependence with stimulant-induced sexual dysfunction
		F15920	Other stimulant dependence with stimulant-induced sleep disorder
		F15921	Other stimulant dependence with other stimulant-induced disorder
		F15922	Other stimulant dependence with unspecified stimulant-induced disorder
		F15929	Other stimulant use, unspecified, uncomplicated
		F1593	Other stimulant use, unspecified with intoxication, uncomplicated
		F1594	Other stimulant use, unspecified with intoxication delirium
		F15950	Other stimulant use, unspecified with intoxication with perceptual disturbance
		F15951	Other stimulant use, unspecified with intoxication, unspecified
		F15959	Other stimulant use, unspecified with withdrawal
		F15980	Other stimulant use, unspecified with stimulant-induced mood disorder
		F15981	Other stimulant use, unspecified with stimulant-induced psychotic disorder with
		F15982	delusions
		F15988	Other stimulant use, unspecified with stimulant-induced psychotic disorder with
		F1599	hallucinations
			Other stimulant use, unspecified with stimulant-induced psychotic disorder, unspecified
			Other stimulant use, unspecified with stimulant-induced anxiety disorder
			Other stimulant use, unspecified with stimulant-induced sexual dysfunction
			Other stimulant use, unspecified with stimulant-induced sleep disorder
			Other stimulant use, unspecified with other stimulant-induced disorder
			Other stimulant use, unspecified with unspecified stimulant-induced disorder
304.50– 304.53 305.30– 305.33	Hallucinogen dependence Nondependent hallucinogen abuse	R783	Finding of hallucinogen in blood
		F1610	Hallucinogen abuse, uncomplicated
		F16120	Hallucinogen abuse with intoxication, uncomplicated
		F16121	Hallucinogen abuse with intoxication with delirium
		F16122	Hallucinogen abuse with intoxication with perceptual disturbance
		F16129	Hallucinogen abuse with intoxication, unspecified
		F1614	Hallucinogen abuse with hallucinogen-induced mood disorder
		F16150	Hallucinogen abuse with hallucinogen-induced psychotic disorder with
		F16151	delusions
		F16159	Hallucinogen abuse with hallucinogen-induced psychotic disorder with
		F16180	hallucinations
		F16183	Hallucinogen abuse with hallucinogen-induced psychotic disorder, unspecified
		F16188	Hallucinogen abuse with hallucinogen-induced anxiety disorder
		F1619	Hallucinogen abuse with hallucinogen persisting perception disorder
		F1620	(flashbacks)

		F1621	Hallucinogen abuse with other hallucinogen-induced disorder
		F16220	Hallucinogen abuse with unspecified hallucinogen-induced disorder
		F16221	Hallucinogen dependence, uncomplicated
		F16229	Hallucinogen dependence, in remission
		F1624	Hallucinogen dependence with intoxication, uncomplicated
		F16250	Hallucinogen dependence with intoxication with delirium
		F16251	Hallucinogen dependence with intoxication, unspecified
		F16259	Hallucinogen dependence with hallucinogen-induced mood disorder
		F16280	Hallucinogen dependence with hallucinogen-induced psychotic disorder with
		F16283	delusions
		F16288	Hallucinogen dependence with hallucinogen-induced psychotic disorder with
		F1629	hallucinations
		F1690	Hallucinogen dependence with hallucinogen-induced psychotic disorder,
		F16920	unspecified
		F16921	Hallucinogen dependence with hallucinogen-induced anxiety disorder
		F16929	Hallucinogen dependence with hallucinogen persisting perception disorder
		F1694	(flashbacks)
		F16950	Hallucinogen dependence with other hallucinogen-induced disorder
		F16951	Hallucinogen dependence with unspecified hallucinogen-induced disorder
		F16959	Hallucinogen use, unspecified, uncomplicated
		F16980	Hallucinogen use, unspecified with intoxication, uncomplicated
		F16983	Hallucinogen use, unspecified with intoxication with delirium
		F16988	Hallucinogen use, unspecified with intoxication, unspecified
		F1699	Hallucinogen use, unspecified with hallucinogen-induced mood disorder
			Hallucinogen use, unspecified with hallucinogen-induced psychotic disorder with delusions
			Hallucinogen use, unspecified with hallucinogen-induced psychotic disorder with hallucinations
			Hallucinogen use, unspecified with hallucinogen-induced psychotic disorder, unspecified
			Hallucinogen use, unspecified with hallucinogen-induced anxiety disorder
			Hallucinogen use, unspecified with hallucinogen persisting perception disorder (flashbacks)
			Hallucinogen use, unspecified with other hallucinogen-induced disorder
			Hallucinogen use, unspecified with unspecified hallucinogen-induced disorder
		F1810	Inhalant abuse, uncomplicated
		F18120	Inhalant abuse with intoxication, uncomplicated
		F18121	Inhalant abuse with intoxication delirium
		F18129	Inhalant abuse with intoxication, unspecified

		F1814	Inhalant abuse with inhalant-induced mood disorder
		F18150	Inhalant abuse with inhalant-induced psychotic disorder with delusions
		F18151	Inhalant abuse with inhalant-induced psychotic disorder with hallucinations
		F18159	Inhalant abuse with inhalant-induced psychotic disorder, unspecified
		F1817	Inhalant abuse with inhalant-induced dementia
		F18180	Inhalant abuse with inhalant-induced anxiety disorder
		F18188	Inhalant abuse with other inhalant-induced disorder
		F1819	Inhalant abuse with unspecified inhalant-induced disorder
		F1820	Inhalant dependence, uncomplicated
		F1821	Inhalant dependence, in remission
		F18220	Inhalant dependence with intoxication, uncomplicated
		F18221	Inhalant dependence with intoxication delirium
		F18229	Inhalant dependence with intoxication, unspecified
		F1824	Inhalant dependence with inhalant-induced mood disorder
		F18250	Inhalant dependence with inhalant-induced psychotic disorder with delusions
		F18251	Inhalant dependence with inhalant-induced psychotic disorder with
		F18259	hallucinations
		F1827	Inhalant dependence with inhalant-induced psychotic disorder, unspecified
		F18280	Inhalant dependence with inhalant-induced dementia
		F18288	Inhalant dependence with inhalant-induced anxiety disorder
		F1829	Inhalant dependence with other inhalant-induced disorder
		F1890	Inhalant dependence with unspecified inhalant-induced disorder
		F18920	Inhalant use, unspecified, uncomplicated
		F18921	Inhalant use, unspecified with intoxication, uncomplicated
		F18929	Inhalant use, unspecified with intoxication with delirium
		F1894	Inhalant use, unspecified with intoxication, unspecified
		F18950	Inhalant use, unspecified with inhalant-induced mood disorder
		F18951	Inhalant use, unspecified with inhalant-induced psychotic disorder with
		F18959	Delusions
		F18980	Inhalant use, unspecified with inhalant-induced psychotic disorder with
		F18988	hallucinations
		F1899	Inhalant use, unspecified with inhalant-induced psychotic disorder, unspecified
			Inhalant use, unspecified with inhalant-induced anxiety disorder
			Inhalant use, unspecified with other inhalant-induced disorder
			Inhalant use, unspecified with unspecified inhalant-induced disorder
292.0	Drug withdrawal	R785	Finding of other psychotropic drug in blood
292.11	Drug-induced psychotic disorder with delusions	R784	Finding of other drugs of addictive potential in blood
292.12	Drug-induced psychotic disorder with hallucinations	F1910	Other psychoactive substance abuse, uncomplicated
292.2	Pathological drug intoxication	F19120	Other psychoactive substance abuse with intoxication, uncomplicated

292.81	Drug-induced delirium	F19121	Other psychoactive substance abuse with intoxication delirium
292.82	Drug-induced persistent dementia	F19122	Other psychoactive substance abuse with intoxication with perceptual
292.83	Drug-induced persistent amnestic disorder	F19129	disturbances
292.84	Drug-induced mood disorder	F1914	Other psychoactive substance abuse with intoxication, unspecified
292.89	Other drug-induced mental disorder	F19150	Other psychoactive substance abuse with psychoactive substance-induced
292.9	Unspecified drug-induced mental disorder	F19151	mood Disorder
		F19159	Other psychoactive substance abuse with psychoactive substance-induced
		F19180	psychotic disorder with delusions
		F19181	Other psychoactive substance abuse with psychoactive substance-induced
		F19182	psychotic disorder with hallucinations
		F19188	Other psychoactive substance abuse with psychoactive substance-induced
		F1919	psychotic disorder, unspecified
		F1920	Other psychoactive substance abuse with psychoactive substance-induced
		F1921	anxiety disorder
		F19220	Other psychoactive substance abuse with psychoactive substance-induced
		F19221	sexual dysfunction
		F19222	Other psychoactive substance abuse with psychoactive substance-induced sleep
		F19229	disorder
		F19230	Other psychoactive substance abuse with other psychoactive substance-induced
		F19231	disorder
		F19232	Other psychoactive substance abuse with unspecified substance-induced
		F19239	disorder
		F1924	Other psychoactive substance dependence, uncomplicated
		F19250	Other psychoactive substance dependence, in remission
		F19251	Other psychoactive substance dependence with intoxication, uncomplicated
		F19259	Other psychoactive substance dependence with intoxication delirium
		F19280	Other psychoactive substance dependence with intoxication with perceptual
		F19281	disturbance
		F19282	Other psychoactive substance dependence with intoxication, unspecified
		F19288	Other psychoactive substance dependence with withdrawal, uncomplicated
		F1929	Other psychoactive substance dependence with withdrawal delirium
		F1990	Other psychoactive substance dependence with withdrawal with perceptual
		F19920	disturbance
		F19921	Other psychoactive substance dependence with withdrawal, unspecified
		F19922	Other psychoactive substance dependence with psychoactive substance-
		F19929	induced mood disorder
		F19930	Other psychoactive substance dependence with psychoactive substance-
		F19931	induced psychotic disorder with delusions
		F19932	

		F19939 F1994 F19950 F19951 F19959 F19980 F19981 F19982 F19988 F1999	Other psychoactive substance dependence with psychoactive substance-induced psychotic disorder with hallucinations Other psychoactive substance dependence with substance-induced psychotic disorder, unspecified Other psychoactive substance dependence with psychoactive substance-induced anxiety disorder Other psychoactive substance dependence with psychoactive substance-induced sexual dysfunction Other psychoactive substance dependence with psychoactive substance-induced sleep disorder Other psychoactive substance dependence with other psychoactive substance induced disorder Other psychoactive substance dependence with unspecified psychoactive substance-induced disorder Other psychoactive substance use, unspecified, uncomplicated Other psychoactive substance use, unspecified with intoxication, uncomplicated Other psychoactive substance use, unspecified with intoxication with delirium Other psychoactive substance use, unspecified with intoxication with perceptual Disturbance Other psychoactive substance use, unspecified with intoxication, unspecified Other psychoactive substance use, unspecified with withdrawal, uncomplicated Other psychoactive substance use, unspecified with withdrawal delirium Other psychoactive substance use, unspecified with withdrawal with perceptual disturbance Other psychoactive substance use, unspecified with withdrawal, unspecified Other psychoactive substance use, unspecified with psychoactive substance induced mood disorder Other psychoactive substance use, unspecified with psychoactive substance induced psychotic disorder with delusions Other psychoactive substance use, unspecified with psychoactive substance induced psychotic disorder with hallucinations Other psychoactive substance use, unspecified with psychoactive disorder, unspecified Other psychoactive substance use, unspecified with anxiety disorder Other psychoactive substance use, unspecified with sexual dysfunction Other psychoactive substance use, unspecified with sleep disorder Other psychoactive substance use, unspecified with other disorder Other psychoactive substance use, unspecified with unspecified disorder
Overdose			

Contributing cause			
		T36-T50 T40	Poisoning by, adverse effect of and underdosing of drugs, medicaments and biological substances
		T40.1X1 T40.2X1A	Poisoning by, adverse effect of and underdosing of narcotics and psychodysleptics
		T40.0	Poisoning by heroin, accidental (unintentional)
		T40.1	Poisoning by other opioids, accidental (unintentional)
		T40.2	Poisoning by Opium
		T40.3	Poisoning by Heroin
		T40.4	Poisoning by Other Opioids
		T40.6	Poisoning by Methadone
		T50.901A	Poisoning by Other Synthetic Narcotics
		T50.902A	Poisoning by Other and Unspecified Narcotics
956.09	Poisoning by other opiates and related narcotics	T50.903A	
E85.2	Poisoning by central nervous system stimulants	T50.904A	Poisoning by unspecified drugs, medicaments and biological substances,
970	Poisoning by sedatives and hypnotics	T50.905A	accidental (unintentional)
967	Poisoning by psychotropic agents	T50.991A	Poisoning by unspecified drugs, medicaments and biological substances,
969	Poisoning by cocaine	T50.992A	accidental (unintentional), initial encounter
E938.5	Poisoning by hallucinogens (psychodysleptics)	T50.993A	Poisoning by unspecified drugs, medicaments and biological substances,
969.6	Accidental poisoning by hallucinogens	T50.994A	intentional self-harm, initial encounter Poisoning by unspecified drugs,
E854.1	(psychodysleptics)	T50.995A	medicaments and biological substances, assault, initial encounter
965.00	Poisoning by opium	T42.6X1A	Poisoning by unspecified drugs, medicaments and biological substances,
965.01	Poisoning by heroin	T65.91XA	undetermined, initial encounter
965.02	Poisoning by methadone		Adverse effect of unspecified drugs, medicaments and biological substances,
965.09	Poisoning by other opiates and related narcotics		initial encounter
E850.0	Heroin poisoning		Poisoning by other drugs, medicaments and biological substances, accidental
E935.0	Heroin, adverse effects		(unintentional), initial encounter
			Poisoning by other drugs, medicaments and biological substances, intentional self-harm, initial encounter
			Poisoning by other drugs, medicaments and biological substances, assault, initial encounter
			Poisoning by other drugs, medicaments and biological substances, undetermined, initial encounter
			Adverse effect of other drugs, medicaments and biological substances, initial encounter
			Poisoning by oth antieplptc and sed-hypntc drugs, acc, init
			Toxic effect of unspecified substance, accidental (unintentional), initial encounter

Intentional self-poisoning			
E950	Suicide and self-inflicted poisoning by solid or liquid substances	X60 X61 X62 X63 X64 X65	Intentional self-poisoning by and exposure to nonopioid analgesics, antipyretics and antirheumatics Intentional self-poisoning by and exposure to antiepileptic, sedative-hypnotic, antiparkinsonism and psychotropic drugs, not elsewhere classified Intentional self-poisoning by and exposure to narcotics and psychodysleptics [hallucinogens], not elsewhere classified Intentional self-poisoning by and exposure to other drugs acting on the autonomic nervous system Intentional self-poisoning by and exposure to other and unspecified drugs, medicaments and biological substances Intentional self-poisoning by and exposure to alcohol
Assault			
E962.0	Assault by drugs and medicinal substances	X85	Assault by drugs, medicaments and biological substances

Table A3 - Diagnostic Codes used to exclude patients from Study Cohort

ICD-9	Diagnosis	ICD-10	Diagnosis
347.10-347.11 327.36	Narcolepsy - symptomatic management Circadian rhythm sleep disorder, shift-work type	G47 G47.419 G47.26	Sleep disorders Narcolepsy without cataplexy Circadian rhythm sleep disorder, shift work type

Attention Deficit Hyperactivity Disorder (ADHD) Safety Edit

Goals:

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

Length of Authorization:

- Up to 12 months

Requires PA:

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

Covered Alternatives:

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

Table 1. FDA-approved and OHP-funded Indications.

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

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

Table 2. Standard Age and Maximum Daily Doses.

Drug Type	Generic Name	Minimum Age	Maximum Age	Maximum Daily Dose (adults or children <18 years of age unless otherwise noted)
CNS Stimulant	amphetamine/dextroamphetamine salts IR	3		40 mg
CNS Stimulant	amphetamine/dextroamphetamine salts ER	6		60 mg
CNS Stimulant	dexmethylphenidate IR	6		20 mg
CNS Stimulant	dexmethylphenidate LA	6		40 mg for adults or 30 mg if age <18 years
CNS Stimulant	dextroamphetamine IR	6		40 mg
CNS Stimulant	dextroamphetamine LA	6		60 mg
CNS Stimulant	lisdexamfetamine	6		70 mg
CNS Stimulant	methamphetamine	6	17	not established
CNS Stimulant	methylphenidate IR	4		60 mg
CNS Stimulant	methylphenidate LA	6		72 mg
CNS Stimulant	methylphenidate transdermal	6	17	30 mg
Non-Stimulant	atomoxetine	6		100 mg
Non-Stimulant	clonidine LA	6	17	0.4 mg
Non-Stimulant	guanfacine LA	6	17	4 mg for adjunctive therapy in ages 6-17 years and for monotherapy in ages 6-12 years 7 mg for monotherapy in ages 13-17 years

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

Table 3. Standard Combination Therapy for ADHD

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

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

* As recommended by the American Academy of Pediatrics 2011 Guidelines www.pediatrics.org/cgi/doi/10.1542/peds.2011-2654

**As identified by Drug Class Review: Pharmacologic Treatments for Attention Deficit Hyperactivity Disorder: Drug Effectiveness Review Project, 2011.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the drug being used to treat an OHP-funded condition?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by OHP.
3. Is the requested drug on the PDL?	**Yes:** Go to #5	**No:** Go to #4
4. Will the prescriber consider a change to a preferred agent? Message: • Preferred drugs are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of preferred alternatives	**No:** Go to #5
5. Is the request for an approved FDA diagnosis defined in Table 1?	**Yes:** Go to #6	**No:** Go to #9
6. Are the patient's age and the prescribed dose within the limits defined in Table 2?	**Yes:** Go to #7	**No:** Go to #9
7. Is the prescribed drug the only stimulant or non-stimulant filled in the last 30 days?	**Yes:** Approve for up to 12 months	**No:** Go to #8
8. Is the multi-drug regimen considered a standard combination as defined in Table 3?	**Yes:** Approve for up to 12 months	**No:** Go to #9

Approval Criteria		
9. Was the drug regimen developed by, or in consultation with, a psychiatrist, developmental pediatrician, psychiatric nurse practitioner, sleep specialist or neurologist?	**Yes:** Document name and contact information of consulting provider and approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness. Doses exceeding defined limits or non-recommended multi-drug regimens of stimulants and/or non-stimulants are only approved when prescribed by a psychiatrist or in consultation with a mental health specialist. May approve continuation of existing therapy once up to 90 days to allow time to consult with a mental health specialist.

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

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Policy Proposal: Retrospective Drug Use Review (DUR) in Schizophrenia Patients

Goals:

1. Identify schizophrenia patients who are non-adherent to routine antipsychotic therapy, and notify their prescribing provider when they miss a medication refill.

Recommendations:

- Recommend implementation of a retrospective initiative to notify providers when patients on routine therapy for schizophrenia miss a medication refill.

Background and Program Description:

In order to improve care for patients with mental health conditions, the Mental Health Clinical Advisory Group (MHCAG), a subcommittee of the Pharmacy and Therapeutics Committee, has developed treatment algorithms for patients with schizophrenia. Medication algorithms emphasize the importance of adherence to treatments and recommend utilization of long-acting injectable formulations to promote adherence to therapies.[1] In an analysis of Oregon Medicaid patients with schizophrenia over 6 months, only 62% of patients were adherent to oral antipsychotic therapy defined as more than 75% of days of coverage.[2] Approximately 12% of patients had less than 45 days of antipsychotic therapy and 26% of patients had less than 135 days of therapy prescribed.[2] In an effort to encourage and promote treatment adherence, the following proposal will notify prescribers when patients who were previously adherent to antipsychotic therapy miss a medication refill.

Patient Selection Criteria:

Patients will be identified according to the following inclusion and exclusion criteria, and notifications will be sent out weekly to the most recent prescriber of the antipsychotic. Patients were included if they had a diagnosis of schizophrenia, were previously adherent to antipsychotic treatment, and had a history of medical visits for mental health conditions. Prescribers are notified if a patient had an interruption in medication therapy of more than 15 days. After a fax is sent, the same provider won't be notified for the same patient and drug for the next 6 months.

Patients are excluded from this program if they lose Medicaid eligibility or have other insurance with drug coverage (e.g., Medicare or primary insurance). If patients have primary insurance with drug coverage, claims data billed to Medicaid is likely incomplete. Members were also excluded if they had subsequent claims for a different antipsychotic drug, indicating that they are transitioning to other therapy or had a sum total of more than 110% of covered days in the 120 days prior to interruption in medication therapy indicating that they may have an excess supply of drug available.

Inclusion criteria:

- Patients currently enrolled in Medicaid (both fee-for-service [FFS] or coordinated care organization [CCO]) with diagnosis of schizophrenia (ICD-10 codes F20xx) within the past 2 years AND

- Patients prescribed continuous oral antipsychotic therapy (PDL classes: antipsychotics, 1st gen or antipsychotics, 2nd gen) defined as claims for the same molecular identity for at least 90 covered days within past 120 days AND
- Patients with an interruption in medication therapy after the most recent paid claim of more than 15 days for the identified drug (defined as drug discontinuation) AND
- Patients with a history of hospitalization or emergency room visit for any psychiatric illness (ICD-10 codes F01xx-F99xx) based on the primary visit diagnosis in the past 2 years

Exclude patients meeting any of the following criteria:

- Patients not currently enrolled in Medicaid or patients who lost Medicaid coverage during interruption in antipsychotic coverage.
- Patients with Medicare or other primary insurance
- Members with a claim for a different oral or injectable antipsychotic drug after the most recent paid antipsychotic prescription (PDL classes: antipsychotics, 1st gen; antipsychotics, 2nd gen; antipsychotics, parenteral)
- Patients with sum of >110% of covered days for specific drug and dose in the past 120 days
- Providers identified as practicing in an emergency setting (specialty provider identification of 247 [emergency med practitioner])
- Providers who have been messaged for the same patient AND drug within the past 6 months

Reporting:

The goal of the program is to improve adherence thereby decreasing unnecessary hospitalizations or emergency department visits. Because billing for medical visits may be delayed by as much as 3 to 12 months, it is difficult to assess ongoing changes in utilization of hospital services for identified members. However, claims data evaluating adherence is reported in a more timely manner and can be reported quarterly on an ongoing basis.

The program will be added to the quarterly retrospective DUR reports with the following reporting parameters:

- Patients identified
- Prescribers identified
- Faxes successfully sent
- Patients with claims for the same antipsychotic within the next 90 days
- Patients with claims for a different antipsychotic within the next 90 days

References:

1. Mental Health Clinical Advisory Group. Schizophrenia. Mental health care guide for licensed practitioners and mental health professionals. Salem, OR: Oregon Health Authority; March 2019. OHA 7548. Available at https://apps.state.or.us/Forms/Served/le7548.pdf. Accessed April 22, 2019.
2. Drug Use Research and Management. Drug Use Evaluation: Antipsychotic Utiilzation in Schizophrenia Patients. March 2019. Available at http://www.orpdl.org/durm/meetings/meetingdocs/2019_03_21/archives/2019_03_21_Schizophrenia_DUE.pdf. Accessed April 22, 2019.

HEALTH SYSTEMS DIVISION
Provider Services
500 Summer St NE
Salem, OR 97301

Date issued: <Month Day, Year>

Voice: 800-336-6016
Fax: 503-945-6873
TTY: 711

<PROVIDER First Name><Last Name>
<1234 MAIN STREET>
<SUITE 100>
<PORTLAND, OR 97227>

For billing ID: «Billing_Provider_Medicaid_ID»

RE: <Generic Drug Name> for <Patient Name> (ID: XXXXXXX) DOB: <MM/DD/YYYY>

Notification of Late Antipsychotic Refill:

- The Oregon Health Authority has developed a safety program to notify prescribers when patients with schizophrenia have not filled their routine antipsychotic prescription as indicated by claims data.
- The patient listed above previously filled an antipsychotic prescription linked to your NPI number and has a history of hospitalization or emergency department visits due to psychiatric illness. They are at least 15 days late filling their antipsychotic medication.
- There may be many reasons for a late refill such as changes in current insurance coverage, hospitalization, changes in lifestyle circumstances, or adverse events leading to treatment discontinuation. Please follow-up with your patient if necessary.

Reason for the safety program:

- Adherence to antipsychotic medications in patients with schizophrenia is strongly correlated with improved treatment outcomes. However, only 65% of Oregon Medicaid patients with schizophrenia are adherent to antipsychotic therapy (with >75% of days covered).
- Recent care guides for schizophrenia emphasize the importance of treatment adherence and recommend use of long-acting injectable antipsychotics, particularly if adherence to therapy is a concern. Use of pillboxes, bubble packing, or other reminder systems may also facilitate patient adherence.
- For further information on treatment recommendations in patients with schizophrenia see the full treatment algorithm recommendations from the Oregon Health Authority Mental Health Clinical Advisory Group, posted at https://apps.state.or.us/Forms/Served/le7548.pdf.

What should you do?

- If you are already aware of this change in drug therapy, there is nothing further you need to do.
- Please follow-up with your patient as appropriate to assess adherence to therapy and reasons for drug discontinuation. Consider patient eligibility for a long-acting injectable antipsychotic.

Questions?

- If you have questions about this message or feedback on this safety program, please contact the Division of Medical Assistance Programs at 503-947-5220.

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Drug Class Update with New Drug Evaluation: Asthma and COPD Maintenance Medications

Date of Review: May 2019

Date of Last Review: January 2018
Dates of Literature Search: 01/01/2014- 02/25/2019
Brand Name (Manufacturer): Yupelri (Mylan)
Dossier Received: yes

Generic Name: Revefenacin

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

Purpose for Class Update:
The purpose of this class update is to provide new comparative effectiveness and safety evidence for asthma and chronic obstructive pulmonary disease (COPD) maintenance medications published since the last review. A new drug evaluation for revefenacin, a long-acting anticholinergic nebulization solution, which was approved in November 2018, will be included.

Research Questions:
1. Is there new comparative evidence on the efficacy/effectiveness of maintenance treatments for asthma and COPD?
2. Is there new comparative evidence of harms associated with maintenance medications used to treat asthma and COPD?
3. Are there subgroups of patients based on demographics (age, racial groups, gender), comorbidities (drug-disease interactions), or other medications (drug-drug interactions) for which maintenance treatments for asthma or COPD differ in efficacy/effectiveness or frequency of adverse events?
4. What is the comparative evidence for efficacy and harms for revefenacin compared to other maintenance treatments for COPD?

Conclusions:
New evidence for this review comes from three new guidelines from the National Institute for Health and Care Excellence (NICE) and Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD), five systematic reviews and meta-analyses from Cochrane Systematic Reviews and Agency for Healthcare Research and Quality (AHRQ), and seven randomized controlled trials.

ASTHMA

Efficacy

- Guidance from NICE supports current policy for Oregon Health Plan (OHP) fee-for-service patients. Treatment recommendations are consistent with prior recommendations with the exception of the use of a leukotriene receptor antagonist (LTRA) in children, 5 and older, and in adults as a second-line treatment option, instead of a long-acting beta-agonists (LABA).[1]

Exacerbations

- In patients 0-4 years of age there is moderate evidence that intermittent inhaled corticosteroid (ICS) in combination with a short-acting beta-agonist (SABA) is more effective than SABA alone at the onset of an upper respiratory infection reduces the risk of needing oral corticosteroids, 38% and 56%, respectively.[2]
- In patients 12 years and older with persistent asthma:
  - There is moderate strength of evidence that risk of exacerbations (composite outcome of requiring systemic corticosteroids, hospitalization or emergency department [ED] visit) was lower with inhaled corticosteroid (ICS) + long-acting beta-agonist (LABA) as controller and quick relief compared to ICS alone, relative risk (RR) 0.64 (95% CI [confidence interval], 0.53 to 0.78; P<0.05) (absolute risk reduction [ARR] not provided).[2] This was also true for ICS + LABA as *controller and quick relief* compared to ICS + LABA as a *controller*, RR 0.68 (95% CI, 0.58 to 0.80; P<0.05;ARR not provided).[2]
  - There is high strength of evidence that the risk of exacerbations requiring corticosteroids is lower with the combination of ICS and a LABA as a *controller and quick relief* compared to the combination of ICS and LABA only as a *controller*. Evidence was of moderate strength for exacerbations requiring ED visits for the same comparison (RR 0.74; 95% CI, 0.59 to 0.93; P<0.05/ARR not reported).[2]
- In patients 12 years and older with uncontrolled asthma and persistent exacerbations the risk of exacerbations requiring systemic corticosteroids was reduced with the combination of LAMA and ICS versus ICS and placebo, 4% vs. 7% (RR 0.67; 95% CI, 48 to 0.92; P<0.05; high strength of evidence).[2]
- The efficacy of using ICS/LABA as controller and quick relief therapy (referred to as single maintenance and reliever therapy [SMART]) compared to ICS with or without LABA controller therapy and SABA for relief therapy in individuals with persistent asthma was studied in a systematic review and meta-analysis. Overall the use of SMART was associated with a lower incidence of exacerbations compared to ICS, with or without LABA, and use of SABA as reliever therapy.[3]

Hospitalizations

- In patients 12 years and older with persistent asthma:
  - The combination of ICS and LABA as a *controller and quick relief* reduced the risk of hospitalizations and ED visits more than ICS and LABA as a *controller* based on high strength of evidence (RR 0.69; 95% CI, 0.63 to 0.76; P<0.05/ARR not reported).[2]

Rescue Medication Use

- The use of rescue medication was reduced with the combination of ICS and LABA as a *controller and quick relief* compared to ICS with or without LABA in patients 12 and older with persistent asthma based on moderate evidence (pooled results not available).[2]

Spirometry

- There is high strength of evidence that long-acting muscarinic antagonists (LAMA) in combination with ICS improves trough forced expiratory volume in one second (FEV1) more than ICS and placebo by a mean difference (MD) of 0.13 L (95% CI, 0.10 to 0.17; P<0.05) in patients 12 years and older with uncontrolled, persistent asthma.[2]
- There was a statistically significant, but most likely not clinically significant, increase in trough FEV1 with the use of ICS and LABA + LAMA compared to ICS and LABA alone (MD 0.07 L ;95% CI, 0.00 to 0.14; P>0.05) based on moderate strength of evidence.[2]

Safety

- A Cochrane systematic review of 14,233 patients found moderate quality evidence of no difference in mortality between salmeterol/ICS compared to ICS (same ICS dose in each group), 11 deaths versus 13 deaths, respectively (odds ratio [OR] 0.80; 95% CI, 0.36 to 1.78).[4] This translates to 1 death per 1000 patients in each group treated for 25 weeks.[4] Recent findings have prompted the Food and Drug Administration (FDA) to remove boxed warning from LABA/ICS products regarding the risks of mortality associated with LABA therapy.[5]

Chronic Obstructive Pulmonary Disease

- Recent guideline updates on the management of COPD support current recommendations.[6,7]

Revefenacin

- Low quality evidence from two short-term, non-published trials demonstrated more trough FEV1 lowering in COPD patients using revefenacin nebulized solution compared to placebo.[8] Limited safety data suggests a similar adverse event profile as other LAMAs. There is insufficient evidence to recommend revefenacin over preferred maintenance treatments for COPD.

Recommendations:

- No changes to the PDL are recommended based on the review of clinical efficacy.
- Recommend clerical revisions to prior authorization (PA) criteria to remove references to guideline classifications of COPD.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy

- Previous reviews have found low to moderate quality evidence of no within-class differences in efficacy or harms for long-acting inhaled (i.e., beta-agonists (LABAs), muscarinic antagonists (LAMAs), or corticosteroids (ICS) and long-acting oral medications (i.e., leukotriene modifiers [LM]) for patients with asthma or COPD. There was insufficient evidence in subgroup populations with asthma or COPD to establish meaningful conclusions on efficacy or harms.
- Preferred therapies for asthma and COPD maintenance medications are:
    a. Anticholinergics: ipratropium (aerosol and solution), tiotropium and ipratropium/albuterol (nebulized solution)
    b. LABA: salmeterol
    c. ICS: budesonide, fluticasone propionate, beclomethasone, fluticasone (Flovent® diskus)
    d. ICS/LABA: fluticasone/salmeterol (diskus and hydrofluoroalkane [HFA]), budesonide/formoterol
    e. LAMA/LABA and LAMA/LABA/ICS combination inhalers: no preferred drugs
- Non-preferred therapies require a prior authorization to verify diagnosis and medical appropriateness.
- There is high utilization (greater than 70%) of preferred therapies in all classes with dedicated preferred options. Maintenance therapies for asthma and COPD represent a substantial cost to OHP, with the LAMA, ICS and LABA/ICS representing the costliest classes.

Background:

ASTHMA

Asthma is a chronic inflammatory condition of the lungs resulting in airway obstruction, bronchial hyperresponsiveness and airway edema. Genetics and environmental factors are thought to contribute to asthma development. A 2013 report on the Burden of Asthma in Oregon cited 3.5-4% of the OHP population as having an asthma diagnosis.[9] Total national asthma costs were projected to be over $20 billion in 2010.[9] Asthma is characterized by symptoms of wheezing, cough, dyspnea and chest tightness. Diagnosis of asthma includes assessment of physical presentation, laboratory evaluation, and confirmation with spirometry (FEV_1 > 200 mL or ≥ 12% from baseline after SABA use). The severity of asthma is differentiated as intermittent or persistent (and further divided into mild, moderate or severe disease).[10]

Asthma treatment can be divided into two categories, quick-relief (rescue) medication and long-term maintenance medications. The Expert Panel Report 3 (EPR3) recommends asthma treatment be approached in a stepwise manner based on the severity of asthma symptoms.[10] Those patients with persistent asthma require long-term control medications to contain the underlying inflammation associated with asthma. Inhaled corticosteroids (ICS) are the preferred maintenance therapy for all patients with persistent asthma. If additional therapy is required to control asthma symptoms, LABAs are most commonly recommended in combination with ICS.[10] Other maintenance therapy options include LTRA, methylxanthines, and cromolyn sodium.

Outcomes used in asthma trials are spirometry (e.g., FEV_1), asthma exacerbations, hospitalization, emergency room visits, and need for oral corticosteroids. Change from baseline in FEV_1 is a common surrogate endpoint used since it is highly reproducible. Minimally important values from research in COPD patients suggest minimally important FEV_1 changes range from 100-140 ml.[11]

COPD

COPD is a chronic respiratory disorder characterized by reduced expiratory flow due to irreversible airway inflammation. Airway narrowing, hyperinflation and impaired gas exchange are pathological changes associated with COPD. The most common cause of COPD is airway irritation, usually from cigarette smoking. In rare cases alpha-1 antitrypsin (AAT) deficiency has been implicated in the development of early onset COPD. It is estimated almost 6% of Oregonians were diagnosed with COPD in 2011. Forty-one percent of these individuals were on at least one daily treatment for COPD.[12] The national incidence of COPD is estimated at 5%, contributing to substantial morbidity and mortality.[13]

Chronic cough or sputum production and dyspnea are common symptoms of COPD. The diagnosis and management of COPD is based on spirometry (post-bronchodilator ratio of FEV1/FVC <0.70), symptom severity, risk of exacerbations and comorbidities.[7] COPD is classified into four stages based on spirometric measurements of FEV1/FVC; grade 1 (mild), grade 2 (moderate), grade 3 (severe), grade 4 (very severe).[7] Therapeutic approaches are often based on disease burden as well as FEV_1, which classifies patients into groups A-D (low to high risk of symptoms and exacerbations).[7] This type of classification system shifts the focus from including just FEV1 measurements, as these are not always indicative of COPD status. Important outcomes to access the effectiveness of therapies include: functional capacity, Quality of Life (QoL) (i.e., St. George's Respiratory Questionnaire [SGRQ]), dyspnea, exacerbation rate and/or severity, mortality and harms. FEV1 is the most common surrogate outcome used in studies to determine therapy effectiveness. Minimally important FEV_1 values for COPD changes have not been clearly defined but are suggested to range from 100-140 ml.[11]

Pharmacotherapy prescribed in a step-wise manner is recommended for COPD management, usually starting with monotherapy and progressing to combination regimens. Short-acting beta-agonists are recommended for acute management and bronchodilator therapy (LABAs and LAMAs) are used as monotherapy or in combination for maintenance treatment for chronic, stable COPD.[7] Inhaled corticosteroids are reserved for patients requiring additional treatment for chronic disease, despite LAMA and LABA therapy. Maintenance reliever therapy (MART) combines ICS and a fast-acting LABA (e.g., formoterol) in a single inhaler for use as maintenance therapy and symptom relief.[6] No treatment has been shown to alter the long-term progression and decline in lung function associated with COPD.[7]

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 – Intermittent Inhaled Corticosteroids and Long-Acting Muscarinic Antagonists for Asthma

AHRQ assessed the efficacy of using intermittent ICS in patients with asthma and to determine if adding a LAMA helps to improve outcomes in patients with uncontrolled, persistent asthma.[2] The review focused on 3 groups: patients 0 to 4 years old with recurrent wheezing, patients 5 years and older with persistent asthma (with or without LABA) and patients 12 years and older with uncontrolled, persistent asthma for the assessment of efficacy of adding a LAMA. Three classes of asthma controllers were included in the review: ICS, LABA and LAMA (**Table 1**). Fifty-six trials were included and were assessed for risk of bias and graded for strength of evidence. Outcomes of interest where exacerbations, mortality, asthma control composite scores, spirometry, asthma-specific quality of life and rescue medication use.[2]

Table 1. Drugs Eligible for Inclusion in AHRQ review[2]

Inhaled Corticosteroids	
beclomethasone budesonide ciclesonide	flunisolide fluticasone mometasone triamcinolone
Long-acting beta-agonists	
arformoterol formoterol	olodaterol salmeterol vilanterol
Long-acting muscarinic antagonists	
aclidinium glycopyrrolate	tiotropium umeclidinium

Results, including ARRs when available, for the three groups of patients and outcomes with moderate to high levels of evidence are presented in **Table 2**. Evidence for patients 0-4 years of age with recurrent wheezing is limited with most outcomes designated as having low strength of evidence or insufficient evidence to prevent conclusions. Outcomes available for analysis in patients 5 to 11 years with persistent asthma had low or insufficient evidence. For patients 12 and older with uncontrolled, persistent asthma, adding a LAMA to an ICS compared to doubling the ICS dose found no difference between treatments based on low strength of evidence for all outcomes of asthma management. This statement was also true for adding a LAMA to ICS compared to adding a LABA to ICS. Mortality rates were too low to draw conclusions regarding safety.

Table 2. Results for Patients with Asthma for Outcomes with Moderate or High Quality Findings[2]

Intervention	Outcome	Results	Strength of Evidence‡
Patients 0-4 Years with Recurrent Wheezing			
Intermittent ICS with SABA as needed **vs.** **SABA as needed***	Reduction in the risk of exacerbation requiring oral corticosteroids	*Favors ICS + SABA* Intermittent ICS + SABA: 70 (38%) SABA: 79 (56%) RR 0.67 (95% CI, 0.46 to 0.98) P<0.05	Moderate
Patients 12 Years or Older with Persistent Asthma			
Intermittent ICS **vs.** **ICS controller**	No difference in QOL∞, spirometry or rescue albuterol use	Pooled results not reported	Moderate to high
ICS + LABA as controller and quick relief **vs.** **ICS†**	Reduction in the risk of exacerbations (composite outcome of requiring systemic corticosteroid, hospitalization or ED visit)	*Favors ICS/LABA as controller and quick relief* RR 0.64 (95% CI, 0.53 to 0.78) P<0.05	Moderate
	Improvement in spirometry	*Favors ICS/LABA as controller and quick relief* MD 0.10 (95% CI, 0.07 to 0.13) P<0.05	Moderate
ICS + LABA as controller and quick relief **vs.** **ICS + LABA as controller†**	Reduction in the risk of exacerbations (composite outcome of requiring systemic corticosteroid, hospitalization or ED visit)	*Favors ICS/LABA as controller and quick relief* RR 0.68 (95% CI, 0.58 to 0.80) P<0.05	High
	Reduction in exacerbations requiring systemic corticosteroids	*Favors ICS/LABA as controller and quick relief* (pooled results not available)	High

	Reduction in exacerbations requiring ED visit	*Favors ICS/LABA as controller and quick relief* RR 0.74 (95% CI, 0.59 to 0.93) P<0.05	Moderate
	Reduction in hospitalization or ED visit	*Favors ICS/LABA as controller and quick relief* RR 0.69 (95% CI, 0.63 to 0.76) P<0.05	High
	Reduction in systemic corticosteroid, hospitalization, ED visit or unscheduled visit	*Favors ICS/LABA as controller and quick relief* RR 0.79 (95% CI, 0.65 to 0.95) P<0.05	Moderate
	Improvement in asthma control scores^	*Favors ICS/LABA as controller and quick relief* RR 1.14 (95% CI, 1.05 to 1.24) P<0.05	Moderate
	No difference in death, mild exacerbations, or spirometry	Not applicable	Moderate
ICS + LABA as controller and quick relief (ICS/LABA Quick) **vs.** **ICS + LABA as controller at a higher ICS dose (ICS/LABA)**	Reduction in the risk of exacerbations (composite outcome of systemic corticosteroid, hospitalization, or ED visit)	*Favors ICS/LABA as controller and quick relief* ICS/LABA Quick: 296 (8.8%) ICS/LABA: 394 (12%) RR 0.75 (95% CI, 0.59 to 0.96) P<0.05	High
	No difference in exacerbations requiring systemic corticosteroid, hospitalizations or ED visits, mild exacerbations, all-cause death, quality of life scores (ACQ-5 and AQLQ[S]), spirometry and rescue medication used	Not applicable	Moderate to high
ICS + LABA as controller and quick relief (ICS/LABA Quick) **vs.** **ICS +/- with or without LABA as a controller (ICS)**	Reduction in the risk of exacerbations (composite outcome of systemic corticosteroid, hospitalization, or ER visit)	*Favors ICS + LABA as controller and quick relief* ICS/LABA Quick: 223 (6.5%) ICS: 238 (8%) RR 0.78 (95% CI, 64 to 0.95) P<0.05	Moderate
	Reduction in rescue medication use	*Favors ICS + LABA as controller and quick relief*	Moderate

		Pooled results not reported	
	Improvement in asthma quality scores	*Favors ICS + LABA as controller and quick relief* Pooled results not reported	Moderate
Patients 12 Years or Older with Uncontrolled, Persistent Asthma			
LAMA + ICS **vs.** **ICS + placebo**	Reduction in risk of exacerbations requiring systemic corticosteroids	*Favors LAMA/ICS* ICS/LABA + LAMA: 86 (4%) ICS/LABA: 74 (7%) RR 0.67 (95% CI, 0.48 to 0.92) P<0.05	High
	Asthma worsening	*Favors LAMA/ICS* ICS/LABA + LAMA: 356 (22%) ICS/LABA: 223 (27%) RR 0.81 (95% CI, 0.68 to 0.97) P<0.05	High
	Improvement in spirometry	*Favors LAMA/ICS* FEV1 trough: MD 0.13 L (95% CI, 0.10 to 0.17) P<0.05	High
	No difference in QOL∞, asthma control scores^, or reduction in medication use	Not applicable	Moderate to high
LAMA + ICS **vs.** **LABA + ICS**	No difference in exacerbations (asthma worsening), asthma control scores^, spirometry or quality of life scores	Not applicable	Moderate to high
	Asthma worsening	*Favors addition of LAMA* ICS/LABA + LAMA: 159 (22%) ICS/LABA: 312 (53%) RR 0.78 (95% CI, 0.72 to 0.86) P<0.05	High
	Improvement in asthma control scores^	Pooled results not available	Moderate-high
	Improvement in spirometry	FEV1 trough MD 0.07 L (95% CI, 0.00 to 0.14) P>0.05	Moderate
	No difference in rescue medication use, exacerbations requiring systemic corticosteroids, exacerbations requiring hospitalizations	Not applicable	Moderate

Key: * At onset of an upper respiratory infection, † Same comparative ICS dose, ‡ Strength of evidence assigned by AHRQ, ^ Asthma Control Scores – composite measure of Asthma Control Test (ACT), Asthma Control Questionnaire (ACQ), various versions, ∞ Asthma-specific QOL scores – Asthma Quality of Life Questionnaire (AQLQ), Pediatric Asthma Quality of Life Questionnaire (PAQLQ), Pediatric Asthma Caregiver's Asthma Quality of Life Questionnaire (PACQLQ)
Abbreviations: ED – emergency department; FEV1 - forced expiratory volume in one second; ICS – inhaled corticosteroids; LABA – long-acting beta-agonists; LAMA – long-acting muscarinic antagonists; MD – mean difference; OR – odds ration; QOL – quality of life; RR – relative risk

Cochrane – Inhaled Steroids with and without regular Salmeterol for Asthma: Serious Adverse Events

A 2018 Cochrane review evaluated the risk of mortality and non-fatal serious adverse events in patients with asthma taking salmeterol and ICS compared to ICS alone (in separate or combined inhalers) for at least 12 weeks.[4] The ICS dose was the same in both comparison groups. A total of 41 studies were included in the review with a majority of subjects taking salmeterol/ICS in one combination inhaler. Main outcomes of interest were death or serious adverse events. Serious adverse events were defined as: death or life-threatening events requiring hospitalization or prolongation of existing hospitalization, resulting in significant disability or incapacity, or resulting in a congenital anomaly/birth defect.

- Out of a total of 14,233 patients included in the analysis, 11 adults taking salmeterol/ICS died compared to 13 taking ICS at the same dose (OR 0.80; 95% CI, 0.36 to 1.78)(moderate evidence).[4] This translates to 1 death per 1000 patients treated in each group treated for 25 weeks. No deaths occurred in children and no deaths in any group were caused by asthma.
- Moderate evidence found adults taking salmeterol/ICS was associated with 332 non-fatal severe adverse events compared to 282 adults receiving regular ICS (OR 1.14; 95% CI 0.97 to 1.33).[4]
- Severe adverse events occurred in 65 children taking salmeterol/ICS compared to 62 children receiving ICS (OR 1.04; 95% CI, 0.73 to 1.48).[4]
- Asthma-related non-fatal severe adverse events were similar between both groups of children, 29 and 23, respectively (moderate quality evidence).

One limitation to this analysis is the absence of death due to asthma in both groups, limiting conclusions on comparative harms. Treatment durations did not exceed 25 weeks which may underestimate adverse events associated with long-term therapy, which is used chronically in patients with asthma.

Cochrane – Umeclidinium Bromide versus Placebo for People with COPD

The focus of a 2017 Cochrane review looked the safety and efficacy of umeclidinium compared to placebo in COPD patients.[14] Patients were a mean age of 60-64 years old with moderate to severe COPD, a 39-52 mean smoking pack-years and baseline FEV1 less than or equal to 70% of predicted normal. There were four studies that met inclusion criteria which lasted 12-52 weeks.[14] For the primary outcome of exacerbations requiring a short course of oral steroid or antibiotic or both, the risk of moderate exacerbations with umeclidinium occurred 55 per 1000 patients less than placebo (OR 0.61; 95% CI, 0.46 to 0.80) (high quality evidence).[14] Therefore, for every 18 people treated with umeclidinium, one additional person was free from a moderate exacerbation (number needed to benefit [NNTB] 18).[14] Moderate quality evidence found umeclidinium to improve the quality of life (based on an improvement of 4 or more on the total score of the SGRQ) in 429 patients per 1000 compared to 342 patients per 1000 taking placebo (OR 1.45; 95% CI, 1.16 to 1.82). Non-fatal serious adverse events were not clinically or statistically different between groups (moderate evidence). Changes in trough FEV1 of 140 ml in umeclidinium treated patients more than placebo,

which was clinically significant (high quality of evidence).[14] Limitations to the review are that all evidence came from manufactured studies lending a high degree of publication bias and the review did not include any active treatment comparisons to provide evidence on comparative effectiveness to other COPD therapies.

Sobieraj, et al – ICS/LABA as Controller and Quick Relief Therapy for Exacerbations and Symptom Control in Persistent Asthma

A 2018 systematic review and meta-analysis reviewed the efficacy of using ICS/LABA as controller and quick relief therapy (SMART) compared to ICS with or without LABA controller therapy and SABA for relief therapy in individuals with persistent asthma.[3] Studies included 22,524 patients that were twelve years of age and older and 341 children ages 4-11 years old. Trials were divided by comparative ICS dose and comparators as follows: SMART versus same dose ICS alone, SMART versus higher dose ICS, SMART versus same dose of ICS and LABA, or SMART versus higher dose of ICS and LABA. All trials but one used budesonide and formoterol for SMART. Included studies were evaluated for risk of bias and the strength of evidence was graded. Main outcomes of interest are asthma exacerbations, use of steroids, hospitalizations, emergency department visits, asthma quality of life, asthma-specific mortality and trough FEV1. Results with moderate or high strength of evidence are reported in **Table 3**. Overall the use of SMART was associated with a lower incidence of exacerbations compared to ICS, with or without LABA, and use of SABA as reliever therapy.

Table 3. SMART versus Other Controller Therapy for Patients with Persistent Asthma 12 years and older[3]

Comparison	Outcome	Results	Strength of Evidence
SMART **Vs.** **Same dose ICS**	Asthma exacerbations*	SMART: 137 (14%) ICS: 212 (22%) ARD -8.1% (95% CI, -11.5 to -4.5) RR 0.64 (95% 0.53 to 0.78) *Favors SMART therapy*	Moderate
	FEV1	SMART: 2.54 L ICS: 2.44 L MD 0.10 L (95% CI, 0.07 to 0.13) *Favors SMART therapy*	Moderate
SMART **Vs.** **Same dose ICS and LABA**	Asthma exacerbations*	SMART: 263 (6%) ICS/LABA: 385 (9%) ARD -6.4% (95% CI, -10.2 to -2.6) RR 0.68 (95% CI, 0.58 to 0.80) *Favors SMART therapy*	High
	Death	SMART: 2 (0.06%) ICS/LABA: 5 (0.15%) ARD -6.4% (95% CI, -10.2 to -2.6) OR 0.43 (95% CI, 0.04 to 4.49) *No difference between treatments*	Moderate
	Patient Response Rate (ACQ-5)†	SMART: 587 (56%)	Moderate

		ICS/LABA: 511 (49%) ARD 6.9% (95% CI, 2.6 to 11.2) RR 1.14 (1.05 to 1.24) *Favors SMART therapy*	
SMART **Vs.** **Higher dose ICS and LABA**	Asthma exacerbations*	SMART: 202 (9%) High ICS/LABA: 394 (12%) ARD: -2.8% (95% CI, -5.2 to -0.3) RR: 0.77 (95% CI, 0.60 to 0.98) *Favors SMART therapy*	High
	Death	SMART: 3 (0.13%) High ICS/LABA: 1 (0.03%) OR 5.19 (95% CI, 0.32 to 85.45) *No difference between treatments*	Moderate
	Asthma control (ACQ-5)	SMART: 1.84 High ICS/LABA: 1.89 MD -0.02 (95% CI, -0.07 to 0.04) *No difference between treatments*	High
	FEV1	SMART: 2.69 L High ICS/LABA: 2.66 L MD 0.01 (-0.3 to 0.04) *No difference between treatments*	Moderate
	Rescue medication use (puffs/day)	SMART: 0.95 High ICS/LABA: 1.01 MD: -0.04 (95% CI, -0.12 to 0.04)	High
Abbreviations: ACQ-5 = Asthma Control Questionnaire; ARD= absolute risk difference; ED = emergency department; ICS = inhaled corticosteroid; LABA = long-acting beta agonist; MD = mean difference, OR = odds ration; RR = risk ratio; SMART = single maintenance and reliever therapy Key: * Required use of systemic corticosteroids, hospitalizations or ED visit, † ACQ-5 responders – patient response was defined as a reduction of 0.5 points or greater			

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

New Guidelines:

High Quality Guidelines:

<u>NICE – Asthma Diagnosis, Monitoring and Chronic Asthma Management</u>

A 2017 NICE guidance updated the management of chronic asthma in children, young people and adults.[1] The pharmacological recommendations will be presented and discussed. Patients who have asthma that is well controlled on their current regimen should not have their treatment changed despite new guideline recommendations. In general, new guidance recommendations mirror previous statements of using SABA first line, followed by an ICS for first-line

maintenance therapy (**Table 4, Table 5 and Table 6**). The addition of an LTRA in children 5 and older and in adults as second-line maintenance therapy, instead of a LABA, is one of the changes to the treatment recommendations.

NICE recommends self-management and titration of ICS doses, up to quadruple the dose if maximum manufacture recommended dose is not exceeded, in adults who use a single inhaler when their asthma symptoms escalate and control deteriorates.[1] Recommendations are the same for children and young people with the exception of limiting the days of increased dose of ICS to 7 days. Maintenance therapy should be accessed and potential decreases in therapy should be considered after at least 3 months of asthma control. Discontinuation of ICS maintenance therapy should only be considered in patients who are symptom free on low dose ICS monotherapy.

Table 4. Pharmacotherapy for Adults (17 years and older) with Newly Diagnosed or Uncontrolled Asthma [1]
Offer a SABA for reliever therapy: SABA monotherapy can be considered for adults who have infrequent, short-lived wheeze and normal lung function.
First-line maintenance therapy is a low dose ICS with the following characteristics: - Symptoms at presentation consistent with need for maintenance therapy (e.g., asthma symptoms 3 or more times a week or causing waking at night) or asthma that is uncontrolled with SABA alone. - In patients with uncontrolled asthma on low dose ICS, offer a leukotriene receptor antagonist (LTRA) in addition to ICS and reevaluate in 4 to 8 weeks. - In patients with uncontrolled asthma on low dose ICS and LTRA, offer a LABA in combination with the ICS, review LTRA therapy to determine response to treatment, and discuss with patient if therapy should be continued.
Patients with uncontrolled asthma on low dose ICS and a LABA, with or without an LTRA, offer a switch the ICS and LABA maintenance therapy to a MART* with low dose maintenance ICS. - If asthma is uncontrolled on MART* regimen with a low dose ICS, with or without LTRA, consider increasing the ICS to a moderate maintenance dose (MART regimen can be continued or switched to a fixed-dose ICS/LABA combination with a SABA as a reliever therapy).
In patients, whose asthma remains uncontrolled on moderate maintenance ICS dose with a LABA (with MART or fixed-dose regimen) with or without a LTRA, consider the following: - Increasing the ICS to high maintenance dose (offered as part of a fixed-dose regimen, with a SABA used as reliever therapy) or a trial of an additional drug (e.g., a LAMA or theophylline) or consultation with asthma expert.
* MART – maintenance and reliever therapy which is a combination of an ICS and fast-acting LABA which is used for daily maintenance treatment and symptom relief.

Table 5. Pharmacotherapy for Children and Young People (5 to 16 year olds) with Newly Diagnosed or Uncontrolled Asthma[1]
SABA should be offered to children and young people with newly diagnosed asthma
SABA monotherapy can be considered for infrequent, short-lived wheeze and normal lung function.
Offer pediatric low dose ICS as first-line maintenance therapy for the following: - Symptoms at presentation consistent with need for maintenance therapy (e.g., asthma symptoms 3 or more times a week or causing waking at night) or asthma that is uncontrolled with SABA alone. - In patients whose asthma remains uncontrolled on a pediatric low dose of an ICS as maintenance therapy, consider an LTRA in addition to the ICS and reevaluate in 4 to 8 weeks.

If asthma remains uncontrolled on pediatric low dose ICS and an LTRA, consider stopping the LTRA and starting a LABA in combination with the ICS.
In patients with uncontrolled asthma on pediatric low dose ICS and LABA, consider changing the regimen to MART* with a pediatric low maintenance ICS dose.
If asthma is uncontrolled on a MART* regimen with a pediatric low maintenance dose ICS, consider increasing the ICS to pediatric moderate maintenance dose (either on a MART regimen or changing to a fixed-dose of an ICS and a LABA, with a SABA as reliever therapy).
If the patient's asthma remains uncontrolled on a pediatric moderate maintenance ICS dose with LABA (either as MART or a fixed-dose regimen) consider seeking advice from an asthma expert or increasing the ICS dose to pediatric high maintenance dose (as part of a fixed-dose regimen, with a SABA used as reliever therapy) or trial of an additional drug (theophylline).
* MART – maintenance and reliever therapy which is a combination of an ICS and fast-acting LABA which is used for daily maintenance treatment and symptom relief.

Table 6. Pharmacotherapy for Children Under 5 with Suspected or Confirmed Asthma.[1]
A SABA should be offered to children with suspected asthma for symptom relief and alongside maintenance therapy.
An 8-week trial of pediatric moderate dose ICS should be considered in children with the following: - Symptoms at presentation consistent with need for maintenance therapy (e.g., asthma symptoms 3 or more times a week or causing waking at night) or asthma that is uncontrolled with SABA alone. - ICS treatment should be stopped after 8-weeks and child's symptoms should be monitored. - Consider an alternative diagnosis if symptoms did not resolve during trial period.
If symptoms resolved but reoccurred within 4 weeks of stopping ICS, then restart pediatric low dose ICS as first-line maintenance therapy.
If symptoms resolved but reoccurred after 4 weeks of stopping ICS, repeat 8-week trial of pediatric moderate dose ICS.
If pediatric low dose ICS maintenance therapy fails to control symptoms in children with suspected asthma, consider an LTRA in addition to an ICS.
If children with suspected asthma remain uncontrolled on pediatric low dose ICS and LTRA maintenance therapy, discontinue LTRA and refer the child to an asthma specialist.

NICE – Chronic Obstructive Pulmonary Disease: Diagnosis and Management

A March 2018 review evaluated the effectiveness of LAMAs, LABAs and ICSs for managing patients with stable COPD.[6] Included patient were over 35 years of age with a baseline FEV1 of less than 80% predicted. The majority of participants were also using an ICS. The main outcomes of interest were: COPD exacerbations, SGRQ scores, transition dyspnea index (TDI), mortality, trough FEV1, pneumonia, dropouts due to adverse events, and serious adverse events. Exacerbations were divided into moderate and severe. The definition of a moderate exacerbation was worsening of respiratory status that requires treatment with systemic corticosteroids and/or antibiotics. Severe exacerbations were defined as those with rapid deterioration requiring hospitalization. FEV1 and TDI were analyzed at 3, 6 and 12 months and all other outcomes were collected at the final time point. Minimal clinically important differences were determined for the following outcomes: total change in SGRQ score (4 points), trough FEV1 (100 ml), change in TDI (1 point). Outcomes with moderate to high strength of evidence will be presented.[6] Network meta-analysis (NMA) comparisons were also done, but results are not included due to the inherent methodological issues with NMAs.

LABA/LAMA versus LABA/ICS

- LABA/LAMA demonstrated a lower risk of pneumonia compared to those patients taking LABA/ICS based on moderate quality evidence.
- Trough FEV1 was improved at 3 and 6 months (but not at 12 months) in more patients taking LAMA/LABA compared to LABA/ICS based on very low to moderate quality evidence, but the differences were not clinically different.
- Other outcomes found no meaningful differences between LABA/LAMA and LABA/ICS.

LABA/LAMA versus LAMA

- No meaningful differences between LABA/LAMA and LAMA were demonstrated based on moderate or high quality evidence.

LABA/LAMA versus LABA

- There was no moderate or high-quality evidence demonstrating differences in outcomes for LABA/LAMA versus LABA.

LABA/ICS versus LAMA

- Low to moderate quality of evidence found reduced incidence of all-cause mortality and cardiac severe adverse reaction associated with LABA/ICS compared to LAMA. Incidence of pneumonia was higher in patients treated with LABA/ICS compared to LAMA based on low to moderate evidence.
- There was low to moderate quality evidence of no meaningful difference in other outcomes.

LABA/ICS versus LABA

- The risk of pneumonia was increased in patients taking LABA/ICS compared to LABA alone based on high quality evidence.
- There was low to high quality evidence of no meaningful difference in other outcomes.

LAMA versus LABA

- A reduction in the number of patients with severe exacerbations and severe adverse events (COPD related) was less in patients taking LAMA compared to LABA; however, these differences did not meet the threshold for being clinically meaningful.
- There was low to moderate quality evidence of no meaningful difference in other outcomes.

LAMA monotherapy (tiotropium, aclidinium, glycopyrronium, or umeclidinium) versus placebo

- ***Tiotropium 5-18 mcg***: In studies evaluating tiotropium to placebo, tiotropium was found to improve trough FEV1 (121 – 134 mL), TDI (1.05-1.10) and number of SGRQ responders (RR 1.33; CI, 1.25 to 1.42; $p<0.00001$) (moderate strength of evidence). Improvements met the threshold for minimal clinically important differences (MCID). Moderate strength of evidence found no differences in the incidence of severe exacerbations or serious adverse events between the groups.
- ***Aclidinium bromide 400 mcg (twice daily)***: Compared to placebo, aclidinium improved TDI and SGRQ scores based on low to high quality of evidence; however, scores did not meet the threshold for being MCID.
- ***Glycopyrronium bromide 50 mcg***: Compared to placebo, glycopyrronium improved trough FEV1 and SGRQ at 3 months (but had no meaningful difference in the number of responders) and reduced moderate to severe exacerbations based on low to moderate evidence.
- ***Umeclidinium bromide 62.5 mcg***: TDI, SGRQ scores, SGRQ responders and trough FEV1 were improved when umeclidinium was compared to placebo (low to high quality evidence).

Additional Guidelines for Clinical Context:

Global Initiative for Chronic Obstructive Lung Disease – 2019

The GOLD guidelines are produced on an annual basis to provide strategies for diagnosis, management and prevention of COPD.[7] The guidelines are funded by sales of documents and resources. Seventy-six percent of GOLD board of directors and science committee have ties to industry, suggesting a high risk for publication bias. Other limitations to the guideline include the absence of the following: diversity in representation from professional groups, patient and public input, external review by experts in the field, and discussion on resource implications/barriers of recommendations. Therefore, guideline recommendations for pharmaceutical management will be provided for clinical context but not relied upon for decisions regarding the PDL.

For initial pharmacological treatment of COPD, GOLD recommendations are outlined in **Figure 1**.[7] There is a lack of high-quality evidence to guide initial drug therapy. There is insufficient evidence to recommend one bronchodilator over another for symptom relief (Group B). Patients in Group B may also be candidates for initiation with two bronchodilators if severe breathlessness is present. Use of the modified Medical Research Council (mMRC) dyspnea questionnaire and COPD assessment test (CAT) are used to predict exacerbations which allows for categorization of patients into groups and assists in initial therapy recommendations.

A higher incidence of pneumonia was demonstrated with ICS use in patients with COPD, requiring consideration of clinical benefit versus risk before initiating. For patients experiencing dyspnea (breathlessness or exercise limitation) on one long-acting bronchodilator, a second bronchodilator should be added and if the patient is on LABA/ICS, a LABA can be added as triple therapy.[7] If patients experience exacerbations on long-acting bronchodilator monotherapy, LABA/LAMA or LABA/ICS is recommended. Consideration of add-on ICS therapy should be based on a peripheral blood level of more than 300 eosinophils/microliter, as these patients are more likely to respond to therapy. Patients with 100 eosinophils/microliter or more may be candidates for LABA/ICS if they have had 2 or more moderate exacerbations per year or a least one severe exacerbation requiring hospitalization in the prior year.[7] Patients taking LABA/LAMAs who are experiencing exacerbations should be considered for LABA/LAMA/ICS (a greater response is expected with a higher eosinophil count, approximately 100 cells/microliter or greater). If patients are unlikely to respond based on low eosinophil count, the addition of roflumilast or azithromycin should be considered. Patients taking LABA/ICS who are experiencing exacerbations can be considered for the addition of a LAMA or switched to a LABA/LAMA. Pharmacotherapy for patients with stable COPD are presented in **Table 7**.

Figure 1. Initial Pharmacological Management of COPD[7]

≥ 2 moderate exacerbations or ≥ 1 leading to a hospitalization	**Group C** LAMA	**Group D** LAMA or LAMA + LABA* or ICS + LABA** * Consider if highly symptomatic (e.g., CAT > 20) ** Consider if eos ≥ 300

0 or 1 moderate exacerbations (not leading to hospital admission)	**Group A** A Bronchodilator (short or long-acting) mMRC 0-1 CAT <10	**Group B** A Long Acting Bronchodilator (LABA or LAMA) mMRC ≥ 2 CAT ≥ 10

Abbreviations: EOS = blood eosinophil count in cells per microliter; mMRC = modified Medical Research Council dyspnea questionnaire; CAT = COPD assessment test

Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. 2019 Report. Available at: [14]*. Accessed February 20, 2019.*

Table 7. GOLD Guidance on the use of Pharmacological Therapies in Stable COPD[7]

Pharmacotherapy	Recommendations	Evidence level
Bronchodilators		
LABAs and LAMAs	Long-acting bronchodilators are preferred over short-acting agents except for patients with occasional dyspnea and for immediate relief of symptoms in patients already on long-acting bronchodilators for maintenance therapy Evidence to show improved lung function, dyspnea, health status and reduction in exacerbation rates LAMAs > LABAs for exacerbation reduction and decreased risk of hospitalizations (Evidence B) Combination therapy increases FEV1 and reduces symptoms more than monotherapy Combination therapy reduces exacerbations more than monotherapy (Evidence B)	Evidence A
Long-acting bronchodilator	Patients may be started on single long-acting bronchodilator therapy or dual long-acting bronchodilator therapy Two bronchodilators should be used in patients with persistent dyspnea on only one bronchodilator	Evidence A
Bronchodilators	Inhaled bronchodilators are recommended over oral bronchodilators	Evidence A
Tiotropium	Improves the effectiveness of pulmonary rehabilitation in increasing exercise performance	Evidence B
Theophylline	Not recommended unless other bronchodilators are not available or not affordable	Evidence B
Anti-inflammatory Therapies		
Monotherapy with ICS	Long-term therapy not recommended	Evidence A
LABA + ICS	Long-term therapy may be considered in patients with a history of exacerbations despite appropriate treatment with long-acting bronchodilators LABA/ICS is more effective than individual components for lung function improvements and health status and exacerbation reduction in patients with moderate to very severe COPD Increased risk of pneumonia especially in those with severe disease	Evidence A
Triple Therapy		
LABA + ICS + LAMA	Improves lung function, symptoms and health status and reduces exacerbations compared to ICS/LABA, LABA/LAMA or LAMA monotherapy	Evidence A
Abbreviations: ICS – inhaled corticosteroids; LABA – long-acting beta-agonists, LAMA – long-acting muscarinic antagonist		

The GOLD guidelines recommend escalation or de-escalation based on patient specific responses. If patients experience a lack of clinical benefit, have adverse reactions, or have some improvement of symptoms, de-escalation should be considered. If patients continue to have dyspnea when on a LABA or LAMA or LABA + ICS, recommendations are to consider combination LABA + LAMA or LABA + LAMA + ICS. If patients are experiencing exacerbations on a LABA or LAMA then a LABA + LAMA or LABA + ICS should be considered. In patients with an eosinophil count greater than 100, consider LABA + LAMA + ICS. In patients with eosinophil counts less than 100, consider roflumilast or azithromycin. Roflumilast and azithromycin should also be considered in patients with high eosinophil counts that are on triple therapy and continue to have exacerbations.

New Formulations or Indications:

Formulations

3/2019 – The combination product aclidinium bromide and formoterol fumarate (Duaklir Pressair) was approved as a twice daily maintenance treatment for patients with COPD (**Table 9**).[15]

1/2019 – The first generic of Advair Diskus, Wixela Inhub (fluticasone propionate/salmeterol inhalation powder), was recently approved for the maintenance treatment of airflow obstruction and reducing exacerbations in patients with COPD and for the treatment of asthma in patients 4 and older.[16]

12/2017 – A new nebulized formulation of glycopyrrolate, Lonhala Magnair, was approved by the FDA for the long-term maintenance treatment of airflow obstruction in patients with COPD (**Table 9**).[17]

Indications

12/2017 - Budesnonide/formoterol (Symbicort) received an indication for the treatment of asthma in patients 6 and older (**Table 9**).[18, 28]

4/2018 – The three-drug combination, fluticasone furoate/umeclidinium/vilanterol (Trelegy Ellipta), had the indication section changed to long-term, once-daily, maintenance treatment of airflow obstruction in patients with COPD and for reduction in exacerbations of COPD in patients with a history of exacerbations.[19]

5/2018- Approval of fluticasone furoate (Arnuity Ellipta) for the use as a maintenance treatment for pediatric asthma patients aged 5 to 11 years.[20]

10/2018 - Tiotropium bromide and olodaterol (Stiolto Respimat) received an expanded indication to treat patients with COPD, including bronchitis and/or emphysema.[21]

New FDA Safety Alerts:

Table 8. Description of New FDA Safety Alerts/Updates

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Long-acting beta agonists[5]	NA	12/2017	Removal of boxed warning from combination LABA/ICS products	FDA review finds no significant increase in risk of serious asthma outcomes used in combination with inhaled corticosteroids.

Mometasone[22]	Asmanex	3/2018	Warnings	Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir): Risk of increased systemic corticosteroid effects. Exercise caution when used with mometasone.

Randomized Controlled Trials:

A total of one hundred citations were manually reviewed from the initial literature search. After further review, 85 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining seven trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 9. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Busse, et al[23] **MC, PG, DB, RCT, NI**	Safety analysis of LABA/ICS vs. ICS 26 weeks	Adolescents (10%) and adults (90%) with persistent asthma n=36,010	Composite of asthma-related intubation or death	LABA/ICS: 119 (0.66%) ICS: 108 (0.60%) RR 1.09 (95% CI, 0.83 to 1.43; P=0.55) *No difference in serious asthma-related events*
Kerwin, et al[24] **(GOLDEN 3)** **MC, DD, DB, RCT, phase 3**	Glycopyrrolate 25 mcg nebulized solution twice daily and Glycopyrrolate 50 mcg nebulized solution twice daily vs. Placebo 12 weeks	Adult patients with moderate to very severe COPD N = 653	Change from baseline in trough FEV1	Glycopyrrolate 25 mcg: 0.105 L Glycopyrrolate 50 mcg: 0.126 L Placebo: - 0.022 L *Favors glycopyrrolate*
Kerwin, et al[24] **(GOLDEN 4)** **MC, DD, DB, RCT, phase 3**	Glycopyrrolate 25 mcg nebulized solution twice daily and Glycopyrrolate 50 mcg nebulized solution twice daily vs. Placebo 12 weeks	Adult patients with moderate to very severe COPD N = 641	Change from baseline in trough FEV1	Glycopyrrolate 25 mcg: 0.084 L Glycopyrrolate 50 mcg: 0.082 L Placebo: 0.007 L *Favors glycopyrrolate*
Lipson, et al[25] **(IMPACT)**	Fluticasone furoate 100 mcg/umeclidinium 62.5 mcg/vilanterol 25 mcg (FUV) vs.	Adult patients with moderate (47%) to severe COPD	Annual rate of moderate or severe COPD exacerbations during treatment	FUV: 0.91/year FV: 1.07/year UV: 1.21/year

MC, PG, DB, RCT, phase 3	Fluticasone furoate 100 mcg/vilanterol 25 mcg (FV) vs. Umeclidinium 62.5 mcg/vilanterol 25 mcg (UV) 52 weeks	N= 10,355		FUV vs. FV RR 0.85 (95% CI, 0.80 to 0.90) P<0.001 *Favors triple therapy over FV* FUV vs. UV RR 0.75 (95% CI, 0.70 to 0.81) P<0.001 *Favors triple therapy over UV*
Lipson, et al[26] **(FULFIL)** **MC, DD, DB, RCT, phase 3**	Fluticasone furoate 100 mcg/umeclidinium 62.5 mcg/vilanterol 25 mcg once daily (FUV) Vs. Budesonide 400 mcg/ formoterol 12 mcg twice daily (BF) 24 weeks	Adults 40 years and older with COPD N= 1,810	Coprimary endpoints change in baseline trough FEV1 and St. George's Respiratory Questionnaire total score at week 24	Trough FEV1 FUV: 142 ml BF: -29 ml MD 171 ml (95% CI, 148 to 194) P<0.001 *Triple therapy is superior to combination therapy* SGRQ FUV: -6.6 units BF: -4.4 units MD −2.2 (95% CI, −3.5 to −1.0) P<0.001 *Triple therapy is superior to combination therapy*
O'Byrne, et al[27] **MC, PG, DB, RCT, phase 3**	Terbutaline 6 mcg as needed + placebo twice daily (T) vs. Budesonide 200 mcg/formoterol 6 mcg as needed + placebo twice daily (BF) vs. Budesonide 200 mcg twice daily + terbutaline as needed (BP) 52 weeks	Patients 12 years and older with mild asthma N=3,849	Number of weeks of well-controlled asthma	T: 31.1% BF: 34.4% BP: 44.4% BF vs. T OR 1.14 (95% CI, 1.00 to 1.3) P = 0.046 *As needed budesonide/formoterol superior to terbutaline as needed* BF vs. BP OR 0.64 (95% CI, 0.57 to 0.73) *As needed budesonide/formoterol inferior to maintenance budesonide*

Pearlman, et al[28] **MC, PG, DB, RCT, phase 3**	Budesonide/formoterol 80/4.5 mcg twice daily vs. Budesonide/formoterol 80/2.25 mcg twice daily vs. Budesonide 80 mcg twice daily 12 weeks	Patients 6 to up to 12 years of age with asthma and previously receiving a medium-dose ICS or ICS/LABA N=279	Change in FEV1 from baseline to 1 hour after dosing	Budesonide/formoterol 80/4.5 mcg: 0.28 L Budesonide/formoterol 80/2.25 mcg: 0.24 L Budesonide 80 mcg: 0.17 L <u>Budesonide/formoterol 80/4.5 mcg vs. budesonide 80 mcg:</u> TD 0.12 L (95% CI, 0.03 to 0.20); P = 0.006 *Budesonide/formoterol 80/4.5 mcg was statistically and moderately clinically superior to budesonide* <u>Budesonide/formoterol 80/2.25 mcg vs. budesonide 80 mcg:</u> TD 0.08 (95% CI, 0.00 to 0.16); P=0.063 *Budesonide/formoterol 80/2.25 mcg twice daily was not clinically or statistically more effective than budesonide alone*
Sethi, et al[29] **(AMPLIFY)** **MC, PG, DB, RCT, phase 3** **NI comparison for aclidinium vs. tiotropium**	Aclidinium/formoterol fumarate 400mcg/12mcg twice daily vs. Aclidinium 400 mcg twice daily vs. Formoterol fumarate 12 mcg twice daily And Aclidinium 400mcg twice daily vs. Tiotropium 18 mcg once daily 24-week	Adult patients with moderate to very symptomatic COPD N=1,594	Co-primary endpoints were change from baseline at week 24 in 1-hour morning post-dose FEV1 (aclidinium/formoterol) vs. aclidinium) and trough FEV1 (aclidinium vs. formoterol) And Change from baseline in trough FEV1 for aclidinium vs. tiotropium	Change in post-dose FEV1: Aclidinium/formoterol fumarate 400mcg/12mcg: 84 mL Aclidinium: 84 mL Formoterol: 92 mL <u>Aclidinium/formoterol vs. formoterol*:</u> 55 mL; P<0.001 <u>Aclidinium/formoterol vs. aclidinium*:</u> 14 mL (NS) <u>Aclidinium/formoterol vs. tiotropium*:</u> 19 mL (NS) Change from baseline trough FEV1: <u>Aclidinium vs. tiotropium*:</u> LS MD 7 mL (95% CI: -21 mL to 35 mL; P=0.6377) *Aclidinium/formoterol was more effective than formoterol for the outcome of trough FEV1 change from baseline.* *Aclidinium was noninferior to tiotropium*

Key: * No confidence intervals provided.
Abbreviations: DB = double blind; DD = double dummy; CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV1= forced expiratory volume in one second; LS = least squares; MC = multi-center; MD = mean difference; NI= noninferiority; NS = not significant; OR = odds ratio; PG = parallel group; RCT = randomized control trial; RR = rate ratio; SGRQ = St. George's Respiratory Questionnaire; TD = treatment difference

NEW DRUG EVALUATION: Revefenacin

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:

There are no published studies available to evaluate the safety and efficacy of revefenacin, therefore, risk of bias could not be accessed. Manufacturer dossier and prescribing material provided evidence for the efficacy summary. Two, 12-week clinical trials were used for the FDA- approval of revefenacin nebulization solution for the maintenance treatment of COPD.[8] Revefenacin was given as a 175 microgram once-daily inhalation solution and compared to placebo in a total of 812 patients. Revefenacin nebulized solution is delivered via a standard jet nebulizer. Both trials were randomized, double-blind, placebo-controlled, parallel-group trials in adult patients 40 year and older (mean age of 64 years) with a history of smoking greater than or equal to 10-pack years. Patients were diagnosed with moderate to very severe COPD, had an FEV1/FVC ratio of 0.7 or less, and 48% were current smokers. Concomitant therapy, if on a stable dose 30 days prior to screening, was allowed and 37% of patients were taking LABA or ICS/LABA. The primary endpoint was change from baseline trough FEV1 at day 85 (mITT population) and secondary endpoint of number of SGRQ responders (an improvement of 4 or more). Revefenacin increased FEV1 more than placebo in both studies with a LS mean difference of 146 mL and 147 mL, in trials 1 and 2, respectively (**Table 10**).[8,30] Changes were considered statistically and clinically significant. FDA review suggests a greater clinical benefit in patients with very severe COPD. Changes in SGRQ scores were higher with revefenacin but considered statistically significant in only the first study, OR 2.11 (95% CI, 1.14 to 3.92).

Table 10. Results from Trials of Revefenacin[8,30,31]

Study	Comparators	Outcome	Result
Placebo-controlled Study	Revefenacin 88mcg daily and Revefenacin 175 mcg daily Vs. Placebo	Trough FEV^1 at day 85	Placebo adjusted change: Revefenacin 88 mcg: 79 mL Revefenacin 175 mcg: 146 mL
Placebo-controlled study	Revefenacin 88mcg daily and Revefenacin 175 mcg daily Vs. Placebo	Trough FEV^1 at day 85	Placebo adjusted change: Revefenacin 88 mcg: 155 mL Revefenacin 175 mcg: 142 mL
Abbreviations: FEV^1= forced expiratory flow volume; mcg = microgram; mL = milliliter			

Limitations to the data include lack of published trials to be evaluated for bias; however, data from the FDA summary suggests low risk of selection and performance bias.[29] The evidence that is available is from short term, 12-week, trials in patients with previous use or current smoking history. Lack of active treatment comparison limits ability to determine role of revefenacin in the management of COPD. Improvements in FEV1 border on clinical significance, which is a trough FEV1 change of 100-140 mL. There is insufficient evidence for use with other LAMAs.

Clinical Safety:

Safety data comes from 1,798 patients with revefenacin exposure of 12-52 weeks.[31] Common adverse reactions were similar to other LAMA products and include cough, nasopharyngitis, upper respiratory tract infection, headache and back pain. No severe adverse events were reported in either group except for COPD exacerbations. Drug discontinuations from adverse events were similar in with revefenacin and placebo, 13% and 19%, respectively.[31]

Table 11. Pharmacology and Pharmacokinetic Properties.[8]

Parameter	
Mechanism of Action	Revefenacin is a long-acting muscarinic antagonist (i.e., anticholinergic)
Oral Bioavailability	NA
Distribution and Protein Binding	218 L Active metabolite: 71% Human plasma: 42%
Elimination	54% feces and 27% urine
Half-Life	22-70 hours
Metabolism	Hydrolysis

Abbreviations: NA = Not applicable

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Appendix 1: Current Preferred Drug List

Anticholinergics, Inhaled

Generic	Brand	Form	PDL
ipratropium bromide	ATROVENT HFA	HFA AER AD	Y
ipratropium bromide	IPRATROPIUM BROMIDE	SOLUTION	Y
tiotropium bromide	SPIRIVA	CAP W/DEV	Y
ipratropium/albuterol sulfate	IPRATROPIUM-ALBUTEROL	AMPUL-NEB	Y
aclidinium bromide	TUDORZA PRESSAIR	AER POW BA	N
umeclidinium bromide	INCRUSE ELLIPTA	BLST W/DEV	N
glycopyrrolate	SEEBRI NEOHALER	CAP W/DEV	N
tiotropium bromide	SPIRIVA RESPIMAT	MIST INHAL	N
glycopyrrolate/neb.accessories	LONHALA MAGNAIR REFILL	VIAL-NEB	N
glycopyrrol/nebulizer/accessor	LONHALA MAGNAIR STARTER	VIAL-NEB	N
ipratropium/albuterol sulfate	COMBIVENT RESPIMAT	MIST INHAL	N

Beta-Agonists, Inhaled Long Acting

Generic	Brand	Form	PDL
salmeterol xinafoate	SEREVENT DISKUS	BLST W/DEV	Y
arformoterol tartrate	BROVANA	VIAL-NEB	N
formoterol fumarate	PERFOROMIST	VIAL-NEB	N
indacaterol maleate	ARCAPTA NEOHALER	CAP W/DEV	N
olodaterol HCl	STRIVERDI RESPIMAT	MIST INHAL	N

Corticosteroids, Inhaled

Generic	Brand	Form	PDL
budesonide	PULMICORT FLEXHALER	AER POW BA	Y
fluticasone propionate	FLOVENT HFA	AER W/ADAP	Y
beclomethasone dipropionate	QVAR	AER W/ADAP	Y
fluticasone propionate	FLOVENT DISKUS	BLST W/DEV	Y
fluticasone propionate	ARMONAIR RESPICLICK	AER POW BA	N
mometasone furoate	ASMANEX	AER POW BA	N

budesonide	BUDESONIDE	AMPUL-NEB	N
budesonide	PULMICORT	AMPUL-NEB	N
fluticasone furoate	ARNUITY ELLIPTA	BLST W/DEV	N
flunisolide	AEROSPAN	HFA AER AD	N
ciclesonide	ALVESCO	HFA AER AD	N
mometasone furoate	ASMANEX HFA	HFA AER AD	N
beclomethasone dipropionate	QVAR REDIHALER	HFA AEROBA	N

Corticosteroids/LABA Combination, Inhaled

Generic	Brand	Form	PDL
fluticasone/salmeterol	ADVAIR DISKUS	BLST W/DEV	Y
fluticasone/salmeterol	ADVAIR HFA	HFA AER AD	Y
budesonide/formoterol fumarate	SYMBICORT	HFA AER AD	Y
fluticasone/salmeterol	AIRDUO RESPICLICK	AER POW BA	N
fluticasone/salmeterol	FLUTICASONE-SALMETEROL	AER POW BA	N
fluticasone/vilanterol	BREO ELLIPTA	BLST W/DEV	N
mometasone/formoterol	DULERA	HFA AER AD	N

LAMA/LABA Combination, Inhalers

Generic	Brand	Form	PDL
fluticasone/umeclidin/vilanter	TRELEGY ELLIPTA	BLST W/DEV	N
glycopyrrolate/formoterol fum	BEVESPI AEROSPHERE	HFA AER AD	N
indacaterol/glycopyrrolate	UTIBRON NEOHALER	CAP W/DEV	N
tiotropium Br/olodaterol HCl	STIOLTO RESPIMAT	MIST INHAL	N
umeclidinium brm/vilanterol tr	ANORO ELLIPTA	BLST W/DEV	N
aclidinium brm/formoterol fum	DUAKLIR PRESSAIR	AER POW	N

Appendix 2: Abstracts of Comparative Clinical Trials

Combined Analysis of Asthma Safety Trials of Long-Acting β_2-Agonists.

Busse WW, Bateman ED, Caplan AL, Kelly HW, O'Byrne PM, Rabe KF, Chinchilli VM.

BACKGROUND: Safety concerns regarding long-acting β_2-agonists (LABAs) in asthma management were initially identified in a large postmarketing trial in which the risk of death was increased. In 2010, the Food and Drug Administration (FDA) mandated that the four companies marketing LABAs for asthma perform prospective, randomized, controlled trials comparing the safety of combination therapy with a LABA plus an inhaled glucocorticoid with that of an inhaled glucocorticoid alone in adolescents (12 to 17 years of age) and adults. In conjunction with the FDA, the manufacturers harmonized their trial methods to allow an independent joint oversight committee to provide a final combined analysis of the four trials.

METHODS: As members of the joint oversight committee, we performed a combined analysis of the four trials comparing an inhaled glucocorticoid plus a LABA (combination therapy) with an inhaled glucocorticoid alone. The primary outcome was a composite of asthma-related intubation or death. Post hoc secondary outcomes included serious asthma-related events and asthma exacerbations.
RESULTS: Among the 36,010 patients in the intention-to-treat study, there were three asthma-related intubations (two in the inhaled-glucocorticoid group and one in the combination-therapy group) and two asthma-related deaths (both in the combination-therapy group) in 4 patients. In the secondary analysis of serious asthma-related events (a composite of hospitalization, intubation, or death), 108 of 18,006 patients (0.60%) in the inhaled-glucocorticoid group and 119 of 18,004 patients (0.66%) in the combination-therapy group had at least one composite event (relative risk in the combination-therapy group, 1.09; 95% confidence interval [CI], 0.83 to 1.43; P=0.55); 2100 patients in the inhaled-glucocorticoid group (11.7%) and 1768 in the combination-therapy group (9.8%) had at least one asthma exacerbation (relative risk, 0.83; 95% CI, 0.78 to 0.89; P<0.001).
CONCLUSIONS:
Combination therapy with a LABA plus an inhaled glucocorticoid did not result in a significantly higher risk of serious asthma-related events than treatment with an inhaled glucocorticoid alone but resulted in significantly fewer asthma exacerbations.

Effect of background long-acting beta$_2$-agonist therapy on the efficacy and safety of a novel, nebulized glycopyrrolate in subjects with moderate-to-very-severe COPD.
Kerwin EM, Tosiello R, Price B, Sanjar S, Goodin T.
BACKGROUND: Phase III studies demonstrated efficacy and safety of nebulized glycopyrrolate inhalation solution (GLY) in subjects with COPD. Secondary analyses were performed to examine the effect of background long-acting beta$_2$-agonist (LABA) use on the efficacy and safety of nebulized GLY.
METHODS :In two 12-week placebo-controlled studies (GOLDEN 3 and GOLDEN 4) and one 48-week, open-label active-controlled study (GOLDEN 5), a total of 2,379 subjects were stratified by background LABA use (LABA-yes: n=861; LABA-no: n=1,518) and randomized to placebo vs GLY 25 or 50 µg twice daily, or GLY 50 µg twice daily vs tiotropium (TIO) 18 µg once daily. Lung function, patient-reported outcomes, exacerbations, and safety were assessed.
RESULTS: Compared with placebo, pooled data from the 12-week studies showed significant improvements from baseline with GLY 25 and 50 µg across LABA subgroups in trough FEV_1 (LABA-yes: 0.101 and 0.110 L; LABA-no: 0.092 and 0.101 L, respectively; P<0.001) and St George's Respiratory Questionnaire total score (SGRQ; LABA-yes: -2.957 and -3.888; LABA-no: -3.301 and -2.073, respectively; P<0.05). Incidence of treatment-emergent adverse events (TEAEs) was similar in LABA subgroups, and lower in GLY 25 µg vs placebo. In the 48-week active-controlled study, GLY and TIO both showed improvement from baseline across LABA subgroups in FEV_1 (LABA-yes: 0.106 and 0.092 L; LABA-no: 0.096 and 0.096 L, respectively) and in SGRQ total score (LABA-yes: -5.190 and -3.094; LABA-no: -4.368 and -4.821, respectively). Incidence of TEAEs was similar between GLY and TIO, and across LABA subgroups. Exacerbation rates were similar across treatments and LABA subgroups, and cardiovascular events of special interest were more frequent in the LABA-no subgroup. Nebulized GLY, combined with LABA, did not generate any additional safety signals.
CONCLUSION: Nebulized GLY demonstrated efficacy and was well tolerated up to 48 weeks in subjects with COPD with/without background LABA.

Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD.
Lipson DA, Barnhart F, Brealey N, Brooks J, Criner GJ, Day NC, Dransfield MT, Halpin DMG, Han MK, Jones CE, Kilbride S, Lange P, Lomas DA, Martinez FJ, Singh D, Tabberer M, Wise RA, Pascoe SJ; IMPACT Investigators.
BACKGROUND: The benefits of triple therapy for chronic obstructive pulmonary disease (COPD) with an inhaled glucocorticoid, a long-acting muscarinic antagonist (LAMA), and a long-acting β_2-agonist (LABA), as compared with dual therapy (either inhaled glucocorticoid-LABA or LAMA-LABA), are uncertain.
METHODS: In this randomized trial involving 10,355 patients with COPD, we compared 52 weeks of a once-daily combination of fluticasone furoate (an inhaled glucocorticoid) at a dose of 100 µg, umeclidinium (a LAMA) at a dose of 62.5 µg, and vilanterol (a LABA) at a dose of 25 µg (triple therapy) with fluticasone furoate-vilanterol (at doses of 100 µg and 25 µg, respectively) and umeclidinium-vilanterol (at doses of 62.5 µg and 25 µg, respectively). Each regimen was administered in a single Ellipta inhaler. The primary outcome was the annual rate of moderate or severe COPD exacerbations during treatment.
RESULTS: The rate of moderate or severe exacerbations in the triple-therapy group was 0.91 per year, as compared with 1.07 per year in the fluticasone furoate-vilanterol group (rate ratio with triple therapy, 0.85; 95% confidence interval [CI], 0.80 to 0.90; 15% difference; P<0.001) and 1.21 per year in the umeclidinium-vilanterol group (rate ratio with triple therapy, 0.75; 95% CI, 0.70 to 0.81; 25% difference; P<0.001). The annual rate of severe exacerbations resulting in hospitalization in the triple-therapy group was 0.13, as compared with 0.19 in the umeclidinium-vilanterol group (rate ratio, 0.66; 95% CI, 0.56 to 0.78; 34% difference; P<0.001). There was a higher incidence of pneumonia in the

inhaled-glucocorticoid groups than in the umeclidinium-vilanterol group, and the risk of clinician-diagnosed pneumonia was significantly higher with triple therapy than with umeclidinium-vilanterol, as assessed in a time-to-first-event analysis (hazard ratio, 1.53; 95% CI, 1.22 to 1.92; P<0.001).
CONCLUSIONS: Triple therapy with fluticasone furoate, umeclidinium, and vilanterol resulted in a lower rate of moderate or severe COPD exacerbations than fluticasone furoate-vilanterol or umeclidinium-vilanterol in this population. Triple therapy also resulted in a lower rate of hospitalization due to COPD than umeclidinium-vilanterol. (Funded by GlaxoSmithKline; IMPACT ClinicalTrials.gov number, NCT02164513 .).

FULFIL Trial: Once-Daily Triple Therapy for Patients with Chronic Obstructive Pulmonary Disease.
Lipson DA, Barnacle H, Birk R, Brealey N, Locantore N, Lomas DA, Ludwig-Sengpiel A, Mohindra R, Tabberer M, Zhu CQ, Pascoe SJ.
RATIONALE: Randomized data comparing triple therapy with dual inhaled corticosteroid (ICS)/long-acting β_2-agonist (LABA) therapy in patients with chronic obstructive pulmonary disease (COPD) are limited.
OBJECTIVES: We compared the effects of once-daily triple therapy on lung function and health-related quality of life with twice-daily ICS/LABA therapy in patients with COPD.
METHODS: The FULFIL (Lung Function and Quality of Life Assessment in Chronic Obstructive Pulmonary Disease with Closed Triple Therapy) trial was a randomized, double-blind, double-dummy study comparing 24 weeks of once-daily triple therapy (fluticasone furoate/umeclidinium/vilanterol 100 μg/62.5 μg/25 μg; ELLIPTA inhaler) with twice-daily ICS/LABA therapy (budesonide/formoterol 400 μg/12 μg; Turbuhaler). A patient subgroup remained on blinded treatment for up to 52 weeks. Co-primary endpoints were change from baseline in trough FEV_1 and in St. George's Respiratory Questionnaire (SGRQ) total score at Week 24.
MEASUREMENTS AND MAIN RESULTS: In the intent-to-treat population (n = 1,810) at Week 24 for triple therapy (n = 911) and ICS/LABA therapy (n = 899), mean changes from baseline in FEV_1 were 142 ml (95% confidence interval [CI], 126 to 158) and -29 ml (95% CI, -46 to -13), respectively, and mean changes from baseline in SGRQ scores were -6.6 units (95% CI, -7.4 to -5.7) and -4.3 units (95% CI, -5.2 to -3.4), respectively. For both endpoints, the between-group differences were statistically significant (P < 0.001). There was a statistically significant reduction in moderate/severe exacerbation rate with triple therapy versus dual ICS/LABA therapy (35% reduction; 95% CI, 14-51; P = 0.002). The safety profile of triple therapy reflected the known profiles of the components.
CONCLUSIONS: These results support the benefits of single-inhaler triple therapy compared with ICS/LABA therapy in patients with advanced COPD. Clinical trial registered with www.clinicaltrials.gov (NCT02345161).

Inhaled Combined Budesonide-Formoterol as Needed in Mild Asthma.
O'Byrne PM, FitzGerald JM, Bateman ED, Barnes PJ, Zhong N, Keen C, Jorup C, Lamarca R, Ivanov S, Reddel HK.
BACKGROUND: In patients with mild asthma, as-needed use of an inhaled glucocorticoid plus a fast-acting β_2-agonist may be an alternative to conventional treatment strategies.
METHODS: We conducted a 52-week, double-blind trial involving patients 12 years of age or older with mild asthma. Patients were randomly assigned to one of three regimens: twice-daily placebo plus terbutaline (0.5 mg) used as needed (terbutaline group), twice-daily placebo plus budesonide-formoterol (200 μg of budesonide and 6 μg of formoterol) used as needed (budesonide-formoterol group), or twice-daily budesonide (200 μg) plus terbutaline used as needed (budesonide maintenance group). The primary objective was to investigate the superiority of as-needed budesonide-formoterol to as-needed terbutaline with regard to electronically recorded weeks with well-controlled asthma.
RESULTS: A total of 3849 patients underwent randomization, and 3836 (1277 in the terbutaline group, 1277 in the budesonide-formoterol group, and 1282 in the budesonide maintenance group) were included in the full analysis and safety data sets. With respect to the mean percentage of weeks with well-controlled asthma per patient, budesonide-formoterol was superior to terbutaline (34.4% vs. 31.1% of weeks; odds ratio, 1.14; 95% confidence interval [CI], 1.00 to 1.30; P=0.046) but inferior to budesonide maintenance therapy (34.4% and 44.4%, respectively; odds ratio, 0.64; 95% CI, 0.57 to 0.73). The annual rate of severe exacerbations was 0.20 with terbutaline, 0.07 with budesonide-formoterol, and 0.09 with budesonide maintenance therapy; the rate ratio was 0.36 (95% CI, 0.27 to 0.49) for budesonide-formoterol versus terbutaline and 0.83 (95% CI, 0.59 to 1.16) for budesonide-formoterol versus budesonide maintenance therapy. The rate of adherence in the budesonide maintenance group was 78.9%. The median metered daily dose of inhaled glucocorticoid in the budesonide-formoterol group (57 μg) was 17% of the dose in the budesonide maintenance group (340 μg).
CONCLUSIONS: In patients with mild asthma, as-needed budesonide-formoterol provided superior asthma-symptom control to as-needed terbutaline, assessed according to electronically recorded weeks with well-controlled asthma, but was inferior to budesonide maintenance therapy. Exacerbation rates with the two budesonide-containing regimens were similar and were lower than the rate with terbutaline. Budesonide-formoterol used as needed resulted in substantially lower glucocorticoid exposure than budesonide maintenance therapy. (Funded by AstraZeneca; SYGMA 1 ClinicalTrials.gov number, NCT02149199 .).

Efficacy and safety of budesonide/formoterol pMDI vs budesonide pMDI in asthmatic children (6-<12 years).

Pearlman DS, Eckerwall G, McLaren J, Lamarca R, Puu M, Gilbert I, Jorup C, Sandin K, Lanz MJ

BACKGROUND: The efficacy and safety of budesonide/formoterol pressurized metered-dose inhaler (pMDI) have been demonstrated in patients with asthma at least 12 years old.

OBJECTIVE: To evaluate the efficacy of 2 formoterol doses added to budesonide as fixed combinations vs budesonidealone in children 6 to younger than 12 years with asthma.

METHODS: This randomized, double-blinded, parallel-group, multicenter study (NCT02091986; CHASE 3) included children 6 to younger than 12 years with asthma previously receiving a medium-dose inhaled corticosteroid (ICS) or an ICS plus a long-acting β_2-agonist. Children symptomatic during a 7-28-day run-in on low-dose ICS, 1 inhalation of budesonide dry powder inhaler 90 µg twice daily (BID), were randomized to receive 2 inhalations of budesonide/formoterol pMDI 80/4.5 µg (160/9 µg) BID (n = 92), budesonide/formoterol pMDI 80/2.25 µg (160/4.5 µg) BID (n = 95), or budesonide pMDI 80 µg (160 µg) BID (n = 92) for 12 weeks.

RESULTS: Change in forced expiratory volume in 1 second from baseline to 1 hour after dosing (primary end point), change in forced expiratory volume in 1 second 15 minutes after dosing, and peak expiratory flow 1 hour after dosing at week 12 were statistically significantly greater for budesonide/formoterol 160/9 µg vs budesonide ($P \leq .015$ for all comparisons), but not for budesonide/formoterol 160/4.5 µg vs budesonide. Bronchodilator effects, evident 15 minutes after the dose on day 1, were maintained at week 12. Incidence of protocol-defined asthma exacerbations and improvements in asthma symptom-related and quality-of-life outcomes were similar across treatments. There were no notable safety differences among treatments.

CONCLUSION: Budesonide/formoterol pMDI 160/9 µg showed statistically significant and clinically meaningful lung function improvements vs budesonide pMDI 160 µg, demonstrating appropriateness as a therapeutic option for children 6 to younger than 12 years with asthma symptomatic on ICS alone.

AMPLIFY: a randomized, Phase III study evaluating the efficacy and safety of aclidinium/formoterol vs monocomponents and tiotropium in patients with moderate-to-very severe symptomatic COPD.

Sethi S, Kerwin E, Watz H, Ferguson GT, Mroz RM, Segarra R, Molins E, Jarreta D, Garcia Gil E.

BACKGROUND: AMPLIFY assessed the efficacy and safety of aclidinium bromide/formoterol fumarate (AB/FF) vs its monocomponents and tiotropium (TIO) in patients with moderate-to-very severe symptomatic COPD (NCT02796677).

METHODS: In this 24-week, Phase III, double-dummy, active-controlled study, symptomatic patients (COPD Assessment Test score ≥10) were randomized to twice-daily AB/FF 400/12 µg, AB 400 µg, or FF 12 µg, or once-daily TIO 18 µg. Co-primary endpoints were change from baseline at week 24 in 1-hour morning post-dose FEV1 (AB/FF vs AB) and in pre-dose (trough) FEV1 (AB/FF vs FF). Non-inferiority of AB vs TIO in pre-dose FEV1 was also an objective. Normalized area under the curve (AUC)0-3/3 h FEV1 and nighttime and early morning symptoms were also assessed. A subgroup participated in a 24-hour serial spirometry sub-study.

RESULTS: A total of 1,594 patients were randomized; 566 entered the sub-study. At week 24, 1-hour post-dose FEV1 significantly improved with AB/FF vs AB, FF, and TIO (84, 84, and 92 mL; all $P<0.0001$). AB/FF significantly improved trough FEV1 vs FF (55 mL, $P<0.001$) and AB was non-inferior to TIO. AB/FF significantly improved AUC0-3/3 h FEV1 vs all comparators ($P<0.0001$) and provided significant improvements in early morning symptoms vs TIO. The 24-hour spirometry demonstrated significantly greater improvements with AB/FF in AUC12-24/12 h vs all comparators, and in AUC0-24/24 h vs FF or TIO at week 24. CONCLUSION: In patients with moderate-to-very severe symptomatic COPD, twice-daily AB/FF significantly improved lung function vs monocomponents and TIO, and early morning symptom control vs TIO.

Appendix 3: Medline Search Strategy

Search Strategy:

#	Searches	Results
1	Ipratropium/ or ipratropium.mp.	2425
2	tiotropium.mp. or Tiotropium Bromide/	1439
3	aclidinium bromide.mp.	137
4	umeclidinium.mp.	139
5	glycopyrrolate.mp. or Glycopyrrolate/	1232
6	salmeterol.mp. or Salmeterol Xinafoate/	2723
7	aformoterol.mp.	1
8	formoterol.mp. or Formoterol Fumarate/	2149
9	indacterol.mp.	2
10	olodaterol.mp.	127
11	Budesonide/ or budesonide.mp.	5389
12	Fluticasone/ or fluticasone.mp.	3964
13	beclomethasone.mp. or Beclomethasone/	3634
14	mometasone.mp. or Mometasone Furoate/	901
15	Budesonide/ or budesonide.mp.	5389
16	flunisolide.mp.	360
17	ciclesonide.mp.	315
18	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	18754
19	limit 18 to (english language and humans)	14898
20	limit 19 to (yr="2017 -Current" and (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review"))	100

Appendix 4: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use YUPELRI™ (revefenacin) inhalation solution safely and effectively. See full prescribing information for YUPELRI (revefenacin) inhalation solution.

YUPELRI (revefenacin) inhalation solution, for oral inhalation
Initial U.S. Approval: 2018

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

YUPELRI (revefenacin) inhalation solution is an anticholinergic indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD).

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

For oral inhalation use only. Do not swallow YUPELRI.

- One 175 mcg vial (3 mL) once daily. (2)
- For use with a standard jet nebulizer with a mouthpiece connected to an air compressor. (2)

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

Inhalation solution in a unit-dose vial for nebulization. Each vial contains 175 mcg/3 mL solution. (3)

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

YUPELRI is contraindicated in patients with hypersensitivity to revefenacin or any component of this product. (4)

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

- Do not initiate YUPELRI in acutely deteriorating COPD or to treat acute symptoms. (5.1)
- If paradoxical bronchospasm occurs, discontinue YUPELRI and institute alternative therapy. (5.2)
- Worsening of narrow-angle glaucoma may occur. Use with caution in patients with narrow-angle glaucoma and instruct patients to contact a healthcare provider immediately if symptoms occur. (5.3)
- Worsening of urinary retention may occur. Use with caution in patients with prostatic hyperplasia or bladder-neck obstruction and instruct patients to contact a healthcare provider immediately if symptoms occur. (5.4)
- Immediate hypersensitivity reactions may occur. If such a reaction occurs, therapy with YUPELRI should be stopped at once and alternative treatments should be considered. (5.5)

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

Most common adverse reactions (incidence greater than or equal to 2% and more common than placebo) include cough, nasopharyngitis, upper respiratory tract infection, headache, and back pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Mylan at 1-877-446-3679 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or [24].

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

- Anticholinergics: May interact additively with concomitantly used anticholinergic medications. Avoid administration of YUPELRI with other anticholinergic-containing drugs. (7.1)
- Transporter-related drug interactions: Coadministration of YUPELRI with OATP1B1 and OATP1B3 inhibitors (e.g. rifampicin, cyclosporine, etc.) may lead to an increase in exposure of the active metabolite. Therefore, coadministration with YUPELRI is not recommended. (7.2., 12.3)

----------USE IN SPECIFIC POPULATION----------

Hepatic impairment: Avoid use of YUPELRI in patients with hepatic impairment. (8.6, 12.3)

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

Revised: 11/20

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

Appendix 5: Key Inclusion Criteria

Population	Patients with asthma or COPD
Intervention	Maintenance therapy with anticholinergics, LABA, ICS and/or combinations of these products
Comparator	Therapies listed above
Outcomes	Exacerbations, spirometry, dyspnea, requirement of oral corticosteroid therapy, hospitalizations, emergency department visits, mortality
Timing	Presentation of symptoms
Setting	Outpatient management

Long-acting Beta-agonists (LABA)

Goals:

- To optimize the safe and effective use of LABA therapy in patients with asthma and COPD.
- Step-therapy required prior to coverage of non-preferred LABA products:
  - Asthma: inhaled corticosteroid and short-acting beta-agonist.
  - COPD: inhaled short-acting bronchodilator.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred LABA products

Covered Alternatives:

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

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

Approval Criteria		
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class	**No:** Go to #3
3. Does the patient have a diagnosis of asthma or reactive airway disease ~~(ICD10 J4520-J4522; J45901-45998)~~?	**Yes:** Go to #6	**No:** Go to #4
4. Does the patient have a diagnosis of COPD ~~(ICD10 J449)~~, mucopurulent chronic bronchitis ~~(ICD10 J41.1)~~ and/or emphysema ~~(ICD10 J439)~~?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review. Chronic bronchitis is unfunded ~~(ICD10 J40, J41.0, J41.8, J42).~~
5. Does the patient have an active prescription for an on-demand short-acting bronchodilator (anticholinergic or beta-agonist)?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
6. Does the patient have an active prescription for an on-demand short-acting beta-agonist (SABA) or an alternative rescue medication for acute asthma exacerbations?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Does the patient have an active prescription for an inhaled corticosteroid (ICS) or an alternative asthma controller medication?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Implementation: *3/1/18; 10/9/15; 8/12; 1/10*

Long-acting Beta-agonist/Corticosteroid Combination (LABA/ICS)

Goals:

- To optimize the safe and effective use of LABA/ICS therapy in patients with asthma and COPD.
- Step-therapy required prior to coverage:
  - Asthma: short-acting beta-agonist and inhaled corticosteroid or moderate to severe persistent asthma.
  - COPD: short-acting bronchodilator and previous trial of a long-acting bronchodilator (inhaled anticholinergic or beta-agonist). Preferred LABA/ICS products do NOT require prior authorization.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred LABA/ICS products

Covered Alternatives:

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

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

Approval Criteria		
2. Will the provider consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform provider of covered alternatives in class	**No:** Go to #3
3. Does the patient have a diagnosis of asthma or reactive airway disease ~~(ICD10 J4520-J4522, J45901-45998)~~?	**Yes:** Go to #7	**No:** Go to #4
4. Does the patient have a diagnosis of COPD ~~(ICD10 J449)~~, mucopurulent chronic bronchitis ~~(ICD10 J41.1)~~ and/or emphysema ~~(ICD10 J439)~~?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review. Chronic bronchitis is unfunded ~~(ICD10 J40, J41.0, J41.8, J42)~~.
5. Does the patient have an active prescription for an on-demand short-acting bronchodilator (anticholinergic or beta-agonist)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is there a documented trial of an inhaled long-acting bronchodilator (anticholinergic or beta-agonist)~~, or alternatively has the patient been assessed with GOLD C/D COPD~~?	**Yes:** Approve for up to 12 months. Stop coverage of all other LABA and ICS inhalers.	**No:** Pass to RPh. Deny; medical appropriateness.
7. Does the patient have an active prescription for an on-demand short-acting beta-agonist (SABA) or an alternative rescue medication for acute asthma exacerbations?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
8. Is there a documented trial of an inhaled corticosteroid (ICS) or does the patient have moderate or ~~to~~ severe persistent asthma ~~(Step 3 or higher per NIH EPR 3)~~?	**Yes:** Approve for up to 12 months. Stop coverage of all other ICS and LABA inhalers.	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: *5/19 (KS), 1/18 (KS); 9/16; 11/15; 9/15; 11/14; 11/13; 5/12; 9/09; 2/06*
Implementation: *3/1/18; 10/13/16; 1/1/16; 1/15; 1/14; 9/12; 1/10*

Long-acting Muscarinic Antagonist/Long-acting Beta-agonist (LAMA/LABA) and LAMA/LABA/Inhaled Corticosteroid (LAMA/LABA/ICS) Combinations

Goals:

- To optimize the safe and effective use of LAMA/LABA/ICS therapy in patients with COPD.
- Step-therapy required prior to coverage:
  - COPD: short-acting bronchodilator and previous trial of a long-acting bronchodilator (inhaled anticholinergic or beta-agonist). Preferred LAMA and LABA products do NOT require prior authorization.

Length of Authorization:

- Up to 12 months

Requires PA:

- All LAMA/LABA and LAMA/LABA/ICS products

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 Code	
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of preferred LAMA and LABA products in each class	**No:** Go to #3
3. Does the patient have a diagnosis of asthma or reactive airway disease ~~(ICD10 J4520-J4522, J45901-45998)~~ without COPD?	**Yes:** Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review.	**No:** Go to #4
4. Does the patient have a diagnosis of COPD ~~(ICD10 J449)~~, mucopurulent chronic bronchitis ~~(ICD10 J41.1)~~ and/or emphysema ~~(ICD10 J439)~~?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review. Chronic bronchitis is unfunded ~~(ICD10 J40, J41.0, J41.8, J42)~~.
5. Does the patient have an active prescription for an on-demand short-acting bronchodilator (anticholinergic or beta-agonist)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
6. Is the request for a LAMA/LABA combination product?	**Yes:** Go to #7	**No:** Go to #8
7. Is there a documented trial of a LAMA or LABA, or alternatively a trial of a fixed dose combination short-acting anticholinergic with beta-agonist (SAMA/SABA) (i.e., ipratropium/albuterol), or ≥ 2 moderate exacerbations or ≥ 1 leading to a hospitalization?	**Yes:** Approve for up to 12 months. Stop coverage of all other LAMA and LABA inhalers or scheduled SAMA/SABA inhalers (PRN SABA or SAMA permitted).	**No:** Pass to RPh. Deny; medical appropriateness.
~~6.~~8. Is the request for a ~~the~~ 3 drug ICS/LABA/LAMA combination product ~~fluticasone furoate, umeclidinium and vilanterol (Trelegy Ellipta)~~ and is there a documented trial of a LAMA and LABA, or ICS and LABA or ICS and LAMA? ~~?~~	**Yes:** Approve for up to 12 months. Stop coverage of all other LAMA, LABA and ICS inhalers.~~Go to #7~~	**No:** Pass to RPh. Deny; medical appropriateness.~~**No:** Go to #8~~
~~7. Has the patient been assessed with GOLD C/D COPD?~~	~~**Yes:** Approve for up to 12 months. Stop coverage of all other LAMA, LABA and ICS inhalers.~~	~~**No:** Pass to RPh. Deny; medical appropriateness.~~
~~• Has the patient been assessed with GOLD C/D COPD?~~	~~**Yes:** Approve for up to 12 months. Stop coverage of all other LAMA and LABA inhalers.~~	~~**No:** Go to #9~~
~~• Is there a documented trial of a LAMA or LABA, or alternatively a trial of a fixed dose combination short-acting anticholinergic with beta-agonist (SAMA/SABA) (i.e., ipratropium/albuterol)?~~	~~**Yes:** Approve for up to 12 months. Stop coverage of all other LAMA and LABA inhalers or scheduled SAMA/SABA inhalers (PRN SABA or SAMA permitted).~~	~~**No:** Pass to RPh. Deny; medical appropriateness.~~

Inhaled Corticosteroids (ICS)

Goals:

- To optimize the safe and effective use of ICS therapy in patients with asthma and COPD.
- Step-therapy required prior to coverage for non-preferred ICS products:
  - Asthma: inhaled short-acting beta-agonist.
  - COPD: short-acting and long-acting bronchodilators (inhaled anticholinergics and beta-agonists). Preferred short-acting and long-acting bronchodilators do NOT require prior authorization. See preferred drug list options at http://www.orpdl.org/drugs/.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred ICS products

Covered Alternatives:

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

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

Approval Criteria		
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #3
3. Is the request for treatment of asthma or reactive airway disease ~~(ICD10 J45.20-J45.22, J45.901-45.998)~~?	**Yes:** Go to #7	**No:** Go to #4
4. Is the request for treatment of COPD ~~(ICD10 J44.9)~~, mucopurulent chronic bronchitis ~~(ICD10 J41.1)~~ and/or emphysema ~~(ICD10 J43.9)~~?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review. Chronic bronchitis is unfunded ~~(ICD10 J40, J41.0, J41.8, J42)~~.
5. Does the patient have an active prescription for an on-demand short-acting bronchodilator (anticholinergic or beta-agonist)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Does the patient have an active prescription for an inhaled long-acting bronchodilator (anticholinergic or beta-agonist)?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
7. Does the patient have an active prescription for an on-demand short-acting beta-agonist (SABA) or an alternative rescue medication for acute asthma exacerbations?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

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OHSU Drug Effectiveness Review Project Summary Report – Migraine Treatment and Prevention

Date of Review: May 2019

Date of Last Review: Triptans: March 2016; Beta-blockers: May 2015; Botulinum Toxins: September 2018; Antiepileptics: January 2019
Literature Search: 10/01/2018-03/18/2019

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

Research Questions:

1. Is there new comparative evidence evaluating treatments or preventative therapies for migraines based on important outcomes (e.g., headache frequency, acute migraine medication use, reduction in number of migraines per month)?
2. Is there new comparative harms data for treatments of migraines (e.g., withdrawals due to adverse events, severe adverse events)?
3. Are there certain sub-populations (based on age, gender, ethnicity, or comorbidities) in which certain migraine treatments are more effective or cause less harm?
4. Is there any comparative evidence between traditional migraine therapies (triptans, botulinum toxins, antiepileptics and beta-blockers) and newer CGRP treatments for migraines?

Conclusions:

- The Drug Effectiveness Review Project (DERP) provided all of evidence for this review. There was very low or low quality of evidence for most outcome comparisons. All but one outcome with moderate quality evidence found no difference between therapies used for migraine treatment or prevention.
    - There is moderate evidence that preventative therapy with propranolol (40-160 mg) was associated with a greater reduction in rescue medication use compared to topiramate 200 mg in adult patients with episodic migraine.
- There is insufficient comparative evidence for efficacy or harms for traditional migraine therapies compared to newer calcitonin gene-related peptide (CGRP) therapies.

Recommendations:

- No changes to the preferred drug list (PDL) are recommended based on review of the evidence for prevention and treatment of migraine.
- Evaluate cost in executive session.

Author: Kathy Sentena, PharmD

Summary of Prior Reviews and Current Policy

- A review done in September 2018 updated the prior authorization (PA) criteria to incorporate Guideline Note 42 amendments allowing for the use of chemodenervation (botulinum toxin) for the treatment of chronic migraine. This policy that went into effect October 2018 which authorized coverage of botulinum toxins for patients with migraine headache that have failed treatment with anticonvulsants, tricyclics and beta-blockers. Renewal of botulinum toxin therapy requires a 7 day or more reduction in headaches from baseline headache frequency. A review in March of 2016 found all triptan formulations to be superior to placebo for migraine relief. A sumatriptan review demonstrated that the subcutaneous injection to be the most effective route of administration. The recommendation was to include an oral, nasal and injectable triptan formulation on the PDL. Preferred triptans are sumatriptan (all formulations) and oral naratriptan. All triptans have quantity limits to ensure appropriate use. Current PA criteria for topiramate requires a 90-day trial with evidence of efficacy for continued use. Overall utilization for the class has high PDL adherence (92% or greater) with minimal financial impact to the Oregon Health Plan (OHP). There have been no recent new recommendations for the use of antiepileptic or beta-blockers for the treatment or prevention of migraine.

Methods:

The February 2019 drug class report on Pharmacological Options for the Prevention and Treatment of Chronic and Episodic Migraines by the Drug Effectiveness Review Project (DERP) at the Pacific Northwest Evidence-based Practice Center at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class.

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

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

Summary Findings:

An analysis of the treatment and prevention of migraine was done by DERP in February 2019.[1] A search ending in October 2018 identified 19 randomized clinical trials in adults and children or adolescents for the prevention and treatment of chronic and episodic migraine. Patients with non-migraine headache types (e.g., tension, cluster, and secondary headaches) were not included. Drugs included from the five following classes are included: anticonvulsants, antidepressants, beta-blockers, triptans, and other (**Table 1**).[1] The calcitonin gene-related peptide (CGRP) biologic medications for migraine were excluded, as they were evaluated in a previous analysis by DERP. Eight of the trials were graded as fair or good quality and 12 were considered poor quality. Prevention of migraine was the focus of 16 of the studies and 3 studies (all of low or very low quality), evaluated the treatment of acute migraine. Chronic migraine is defined as 15 or more days of headache per month, lasting at least 3 months, and having migraine features at least 8 days per month. Episodic migraine is considered a subclassification of migraine that is not considered chronic. The main outcomes of interest were migraine events, pain, other symptoms and adverse events.

Table 1. Migraine Treatments Included in the DERP Report[1]

Therapeutic Class	Drug or Drug Combination
Anticonvulsants	• Carbamazepine (e.g., Carbatrol, Epitol, Equetro, Tegretol) • Divalproax (e.g., Depakote) • Topiramate (e.g., Qudexy XR, Topamax, Trokendi XR)

	• Valproic acid and derivatives (e.g., Depakene)
Antidepressants	• Amitriptyline (generic) • Venlafaxine (e.g., Depakene)
Beta-blockers	• Atenolol (e.g., Tenormin) • Metoprolol (e.g., Lopressor) • Nadolol (e.g., Corgard) • Nebivolol (e.g., Bystolic) • Propranolol (e.g., Hemangeol, Inderal, InnoPran XL) • Timolol (e.g., Betimol, Istalol, Timoptic)
Tripatans	• Almotriptan (Axert) • Eletriptan (Relpax) • Frovatriptan (Frova) • Naratriptan (Amerge) • Rizatriptan (Maxalt, Maxalt-MLT) • Sumatriptan (e.g., Imitrex, Onzetra Xsail, Zembrace SymTouch) • Zolmitriptan (Zomig, Zomig-ZMT)
Other	• Dihyrdoergotamine (D.H.E. 45, Migranal) • Ergotamine (Ergomar) • OnabotulinumtoxinA (Botox)
Combination Therapies	• Acetaminophen, aspirin, and caffeine (generic) • Acetaminophen, caffeine, and isometheptene and dichloraphenazone (generic) • Acetaminophen, isometheptene, and dichloralphenazone (generic) • Ergotamine and caffeine (Cafergot, Migergot) • Sumatriptan and naproxen (Treximet)

Chronic Migraines

Four studies evaluated the treatment of chronic migraines.[1] Efficacy and harms comparisons of treatments for chronic migraines demonstrated similar efficacy and harms data, all based on very low or low quality evidence. There was insufficient evidence for outcomes related to the prevention of chronic migraine in children or treatment of chronic migraine in adults, adolescents or children (all very low or low quality of evidence).

Episodic Migraines

Thirteen studies were used for the analysis of episodic migraine.[1] Studies were divided into treatment and prevention groups. There was moderate quality evidence for three outcomes for the *prevention* of episodic migraines: number of migraines per month, withdrawals due to adverse events and days with acute migraine medication use per month (**Table 2**). The outcomes were downgraded for unclear methods of randomization, allocation concealment and conflicts of interest.

Table 2. Therapies for the Prevention of Episodic Migraines in Adults[1]

Comparison	Outcome	Findings*	Quality of Evidence
Topiramate (25 mg to 200 mg) vs. amitriptyline (10-150 mg/day)	Migraine days per month	Trial 1 – Topiramate: -2.6 days Amitriptyline: -2.7 days P=0.87 Trial 2 – Topiramate: 0.65 Amitriptyline: 0.91 P>0.05 *No significant difference*	Moderate
	Withdrawals due to adverse events	Trial 1 – Topiramate: 19.7% Amitriptyline: 22.5% P=0.52 Trial 2- Topiramate: 8.3% Amitriptyline: 14.2% P=0.50 *No significant difference*	Moderate
Topiramate (25 mg to 200 mg/day) vs. Propranolol (40 mg to 160 mg/day)	Days with acute migraine medication use per month	Topiramate 100 mg: -1.5 Topiramate 200 mg: -0.9 Propranolol: -1.6 P=0.74 (topiramate 100 vs. propranolol) P=0.02 (topiramate 200 vs. propranolol) *Propranolol associated with a greater reduction in rescue medication use compared to topiramate 200 mg but not compared to topiramate 100 mg*	Moderate
* Confidence intervals were not provided			

Mixed Migraine Populations – chronic and episodic

Two studies analyzed the prevention of mixed migraines (chronic and episodic).[1] Comparisons in adults were found to be of very low quality, therefore, conclusions could not be drawn. Trials done in children and adolescents were found to have moderate quality of evidence for the comparison of topiramate versus amitriptyline (**Table 3**).

Table 3. Outcomes for Therapies used for Mixed Migraine[1]

Comparison	Outcome	Findings*	Quality of Evidence
Topiramate (2 mg/kg/day) vs. amitriptyline (1 mg/kg/day)	Migraine days per month	Absolute change: Topiramate: -6.7 days Amitriptyline: -6.7 days MD -0.1 (98.3% CI, -1.7 to 1.5) *No significant difference*	Moderate
	Percentage with at least 50% reduction in the number of migraine days per month	Topiramate: 55% Amitriptyline: 52% Adjusted OR 1.14 P>0.05 *No significant difference*	Moderate
	Serious adverse events	Topiramate: 4 Amitriptyline: 6 P>0.05 *No significant difference*	Moderate
	Withdrawals due to adverse events	Topiramate: 22% Amitriptyline: 20% P=0.76 *No significant difference*	Moderate
* Confidence intervals were not provided			

References:

1. Suggested citation: Lazur B, Harrod C. *Pharmacological options for the prevention and treatment of chronic and episodic migraines.* Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2019.

Appendix 1: Current Preferred Drug List

Triptans, Nasal

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

Triptans, Oral

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

Triptans, Subcutaneous

Generic	Brand	Form	PDL
sumatriptan succinate	IMITREX	CARTRIDGE	Y
sumatriptan succinate	SUMATRIPTAN SUCCINATE	CARTRIDGE	Y
sumatriptan succinate	ALSUMA	PEN INJCTR	Y
sumatriptan succinate	IMITREX	PEN INJCTR	Y
sumatriptan succinate	SUMATRIPTAN SUCCINATE	PEN INJCTR	Y

sumatriptan succinate	IMITREX	VIAL	Y
sumatriptan succinate	SUMATRIPTAN SUCCINATE	VIAL	Y
sumatriptan succinate	SUMAVEL DOSEPRO	NDL FR INJ	N
sumatriptan succinate	ZEMBRACE SYMTOUCH	PEN INJCTR	N
sumatriptan succinate	SUMATRIPTAN SUCCINATE	SYRINGE	N

Botulinum Toxins

Generic	Brand	Form	PDL
abobotulinumtoxinA	DYSPORT	VIAL	
incobotulinumtoxinA	XEOMIN	VIAL	N
incobotulinumtoxinA	XEOMIN	VIAL	
onabotulinumtoxinA	BOTOX	VIAL	
onabotulinumtoxinA	BOTOX COSMETIC	VIAL	
onabotulinumtoxinA	BOTOX COSMETIC	VIAL	
rimabotulinumtoxinB	MYOBLOC	VIAL	

Antiepileptics

Generic	Brand	Form	PDL	Carveout
carbamazepine	CARBAMAZEPINE	ORAL SUSP	Y	
carbamazepine	TEGRETOL	ORAL SUSP	Y	
carbamazepine	CARBAMAZEPINE	TAB CHEW	Y	
carbamazepine	CARBAMAZEPINE ER	TAB ER 12H	Y	
carbamazepine	TEGRETOL XR	TAB ER 12H	Y	
carbamazepine	CARBAMAZEPINE	TABLET	Y	
carbamazepine	EPITOL	TABLET	Y	
carbamazepine	TEGRETOL	TABLET	Y	
divalproex sodium	DEPAKOTE SPRINKLE	CAP DR SPR	Y	Y
divalproex sodium	DIVALPROEX SODIUM	CAP DR SPR	Y	Y
divalproex sodium	DEPAKOTE ER	TAB ER 24H	Y	Y
divalproex sodium	DIVALPROEX SODIUM ER	TAB ER 24H	Y	Y
divalproex sodium	DEPAKOTE	TABLET DR	Y	Y
divalproex sodium	DIVALPROEX SODIUM	TABLET DR	Y	Y
topiramate	TOPAMAX	TABLET	Y	
topiramate	TOPIRAMATE	TABLET	Y	
valproic acid	DEPAKENE	CAPSULE	Y	Y
valproic acid	VALPROIC ACID	CAPSULE	Y	Y
valproic acid (as sodium salt)	DEPAKENE	SOLUTION	Y	Y
valproic acid (as sodium salt)	VALPROIC ACID	SOLUTION	Y	Y
topiramate	TROKENDI XR	CAP ER 24H	N	

topiramate	QUDEXY XR	CAP SPR 24	N
topiramate	TOPIRAMATE ER	CAP SPR 24	N
topiramate	TOPAMAX	CAP SPRINK	N
topiramate	TOPIRAMATE	CAP SPRINK	N

Beta-Blockers

Generic	Brand	Form	PDL
atenolol	ATENOLOL	TABLET	Y
atenolol	TENORMIN	TABLET	Y
metoprolol succinate	METOPROLOL SUCCINATE	TAB ER 24H	Y
metoprolol succinate	TOPROL XL	TAB ER 24H	Y
metoprolol tartrate	LOPRESSOR	TABLET	Y
metoprolol tartrate	METOPROLOL TARTRATE	TABLET	Y
propranolol HCl	PROPRANOLOL HCL	TABLET	Y
metoprolol succinate	KAPSPARGO SPRINKLE	CAP SPR 24	N
nadolol	CORGARD	TABLET	N
nadolol	NADOLOL	TABLET	N
nebivolol HCl	BYSTOLIC	TABLET	N
propranolol HCl	INDERAL XL	CAP ER 24H	N
propranolol HCl	INNOPRAN XL	CAP ER 24H	N
propranolol HCl	INDERAL LA	CAP SA 24H	N
propranolol HCl	PROPRANOLOL HCL ER	CAP SA 24H	N
propranolol HCl	HEMANGEOL	SOLUTION	N
propranolol HCl	PROPRANOLOL HCL	SOLUTION	N
timolol maleate	BLOCADREN	TABLET	N
timolol maleate	TIMOLOL MALEATE	TABLET	N

Other Analgesics

Generic	Brand	Route	Form	PDL
butalb/acetaminophen/caffeine	BUTALBITAL-ACETAMINOPHEN-CAFFE	PO	CAPSULE	N
butalb/acetaminophen/caffeine	CAPACET	PO	CAPSULE	N
butalb/acetaminophen/caffeine	ESGIC	PO	CAPSULE	N
butalb/acetaminophen/caffeine	FIORICET	PO	CAPSULE	N
butalb/acetaminophen/caffeine	ZEBUTAL	PO	CAPSULE	N
butalb/acetaminophen/caffeine	VANATOL LQ	PO	SOLUTION	N
butalb/acetaminophen/caffeine	VANATOL S	PO	SOLUTION	N
butalb/acetaminophen/caffeine	AMERICET	PO	TABLET	N
butalb/acetaminophen/caffeine	BUTALBITAL-ACETAMINOPHEN-CAFFE	PO	TABLET	N
butalb/acetaminophen/caffeine	ESGIC	PO	TABLET	N
butalb/acetaminophen/caffeine	QUALA-CET	PO	TABLET	N

butalbital/acetaminophen	BUTALBITAL-ACETAMINOPHEN	PO	CAPSULE	N
butalbital/acetaminophen	ALLZITAL	PO	TABLET	N
butalbital/acetaminophen	BUPAP	PO	TABLET	N
butalbital/acetaminophen	BUTALBITAL-ACETAMINOPHEN	PO	TABLET	N
butalbital/acetaminophen	MARTEN-TAB	PO	TABLET	N
butalbital/acetaminophen	REPAN-CF	PO	TABLET	N
butalbital/aspirin/caffeine	BUTALBITAL-ASPIRIN-CAFFEINE	PO	CAPSULE	N
butalbital/aspirin/caffeine	FIORINAL	PO	CAPSULE	N
butalbital/aspirin/caffeine	BUTALBITAL-ASPIRIN-CAFFEINE	PO	TABLET	N
acetaminophen/caffeine	EXCEDRIN TENSION HEADACHE	PO	TABLET	
acetaminophen/caffeine	TENSION HEADACHE	PO	TABLET	
acetaminophen/caffeine	TENSION HEADACHE RELIEF	PO	TABLET	
ASA/acetaminophen/caffeine/cal	SUPAC	PO	TABLET	
aspirin/acetaminophen/caffeine	EXCEDRIN EXTRA STRENGTH	PO	TABLET	
aspirin/acetaminophen/caffeine	EXCEDRIN MIGRAINE	PO	TABLET	
aspirin/acetaminophen/caffeine	EXTRA PAIN RELIEF	PO	TABLET	
aspirin/acetaminophen/caffeine	HEADACHE PAIN	PO	TABLET	
aspirin/acetaminophen/caffeine	HEADACHE RELIEF	PO	TABLET	
aspirin/acetaminophen/caffeine	MIGRAINE FORMULA	PO	TABLET	
aspirin/acetaminophen/caffeine	MIGRAINE RELIEF	PO	TABLET	
aspirin/acetaminophen/caffeine	PAIN RELIEVER PLUS	PO	TABLET	
aspirin/caffeine	AA & C	PO	TABLET	
aspirin/caffeine	BACK-BODY PAIN RELIEVER	PO	TABLET	
dihydroergotamine mesylate	D.H.E.45	IJ	AMPUL	
dihydroergotamine mesylate	DIHYDROERGOTAMINE MESYLATE	IJ	AMPUL	
dihydroergotamine mesylate	DIHYDROERGOTAMINE MESYLATE	NS	SPRAY/PUMP	
dihydroergotamine mesylate	MIGRANAL	NS	SPRAY/PUMP	
ergotamine tartrate	ERGOMAR	SL	TAB SUBL	
ergotamine tartrate/caffeine	CAFERGOT	PO	TABLET	
ergotamine tartrate/caffeine	MIGERGOT	RC	SUPP.RECT	

Appendix 2: Search History

Database(s): **Ovid MEDLINE(R)** 1946 to March Week 3 2019

Search Strategy:

#	Searches	Results
1	sumatriptan.mp. or Sumatriptan/	2938
2	zolmitriptan.mp.	577
3	succinate.mp. or Succinic Acid/	32032
4	naratriptan.mp.	314
5	rizatriptan.mp.	467
6	almotriptan.mp.	255
7	frovatriptan.mp.	186
8	eletriptan.mp.	266
9	abobotulinumtoxinA.mp.	275
10	rimabotulinumtoxinB.mp.	576
11	incobotulinumtoxinA.mp.	274
12	onabotulinumtoxinA.mp.	592
13	topiramate.mp. or Topiramate/	4105
14	propranolol.mp. or Propranolol/	43276
15	butalbital.mp.	147
16	dihydroergotamine.mp. or Dihydroergotamine/	1839
17	ergotamine.mp. or Ergotamine/	2876
18	migraine.mp. or Migraine Disorders/	32782
19	limit 18 to (english language and humans)	26160
20	limit 19 to yr="2018 -Current"	749
21	limit 20 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	46

Topiramate

Goal(s):

- Approve topiramate only for funded diagnoses which are supported by the medical literature (e.g. epilepsy and migraine prophylaxis).

Length of Authorization:

- 90 days to lifetime

Requires PA:

- Non-preferred topiramate products

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have diagnosis of epilepsy?	**Yes:** Approve for lifetime (until 12-31-2036)	**No:** Go to #3
3. Does the patient have a diagnosis of migraine?	**Yes:** Approve for 90 days with subsequent approvals dependent on documented positive response for lifetime*	**No:** Go to #4
4. Does the patient have a diagnosis of bipolar affective disorder or schizoaffective disorder?	**Yes:** Go to #5	**No:** Go to #6

Approval Criteria		
5. Has the patient tried or are they contraindicated to at least two of the following drugs? • Lithium • Valproate and derivatives • Lamotrigine • Carbamazepine • Atypical antipsychotic Document drugs tried or contraindications.	**Yes:** Approve for 90 days with subsequent approvals dependent on documented positive response for lifetime approval.*	**No:** Pass to RPh; Deny; medical appropriateness. Recommend trial of 2 covered alternatives.
6. Is the patient using the medication for weight loss? (Obesity ICD10 E669; E6601)?	**Yes:** Pass to RPh. Deny; not funded by the OHP	**No:** Pass to RPh. Go to #7
7. All other indications need to be evaluated for appropriateness: • Neuropathic pain • Post-Traumatic Stress Disorder (PTSD) • Substance abuse	Use is off-label: Deny; medical appropriateness. Other treatments should be tried as appropriate. Use is unfunded: Deny; not funded by the OHP. If clinically warranted: Deny; medical appropriateness. Use clinical judgment to approve for 1 month to allow time for appeal. MESSAGE: "Although the request has been denied for long-term use because it is considered medically inappropriate, it has also been APPROVED for one month to allow time for appeal."	

P&T Review: *5/19; 1/19 (DM); 7/18; 3/18; 3/17; 7/16; 3/15; 2/12; 9/07; 11/07*
Implementation: *4/18/15; 5/12, 1/12*

Botulinum Toxins

Goal(s):
- Approve botulinum toxins for funded OHP conditions supported by evidence of benefit.
- Require positive response to therapy for use in chronic migraine headaches or overactive bladder.

Length of Authorization:
- From 90 days to 12 months

Requires PA:

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

Covered Alternatives:

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

Approval Criteria		
1. Is this a request for renewal of a previously approved prior authorization for management of migraine headache or detrusor over-activity (e.g., overactive bladder)?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code	
3. Is botulinum toxin treatment for any of the following? a. Upper or lower limb spasticity (G24.02, G24.1, G35, G36.0, I69.03- I69.06 and categories G71, and G80-G83); b. Strabismus due to a neurological disorder (H50.89); c. Blepharospasm (G24.5); d. Spasmodic torticollis (G24.3); e. Torsion dystonia (G24.9); or f. Achalasia (K22.0).	**Yes:** Approve for up to 12 months	**No:** Go to #4
4. Is botulinum toxin treatment for chronic migraine, with ≥15 headache days per month, of which ≥8 days are with migraine?	**Yes:** Go to #5	**No:** Go to #8
5. Is the botulinum toxin administered by, or in consultation with, a neurologist or headache specialist?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
6. Has the patient had an inadequate response, or has contraindications, to at least 3 pharmacological prophylaxis therapies? • Beta-blockers • Tricyclic antidepressants • Anticonvulsants	**Yes:** Go to #7 Baseline headaches/month: _____.	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of preferred alternatives at www.orpdl.org/drugs/
7. Do chart notes indicate headaches are due to medication overuse?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve no more than 2 injections given ≥3 months apart. Additional treatment requires documented positive response to therapy from baseline (see Renewal Criteria).
8. Is botulinum toxin treatment for idiopathic or neurogenic detrusor over-activity (ICD10-CM N32.81)?	**Yes:** Go to #9	**No:** Pass to RPh. Go to #10
9. Has the patient had an inadequate response to, or is intolerant of, ≥2 incontinence anti-muscarinic drugs (e.g., fesoterodine, oxybutynin, solifenacin, darifenacin, tolterodine, or trospium)?	**Yes:** • Baseline urine frequency/day: _____. • Baseline urine incontinence episodes/day: _____. Approve for up to 90 days. Additional treatment requires documented positive response to therapy from baseline (see Renewal Criteria).	**No:** Pass to RPh. Deny; medical appropriateness.

10. RPh only: Medical literature with evidence for use in funded conditions must be submitted and determined to be appropriate for use before approval is granted.

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

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

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

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

Antimigraine - Triptans

Goal(s):
- Decrease potential for medication overuse headache through quantity limits and therapeutic duplication denials.
- Promote PDL options.

Length of Authorization:
- Up to 6 months

Requires PA:
- Non-preferred drugs

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

Check the Reason for PA:
- Non-Preferred drugs will deny on initiation
- Preferred drugs will deny only when maximum dose exceeded
- Both will deny for concurrent therapy (concurrent triptans by different routes is allowed)

Quantity Limits per Labeling.

Generic	Brand	Max Daily Dose	Dosage Form	Quantity Limit Per Month
Almotriptan	Axert	25 mg	6.25 mg tab 12.5 mg tab	12 tabs
Eletriptan	Relpax	80 mg	20 mg tab 40 mg tab (blister pack 6, 12)	6 tabs
Frovatriptan	Frova	7.5 mg	2.5 mg tab (blister pack 9)	9 tabs
Naratriptan	Amerge	5 mg	1 mg tab 2.5 mg tab (blister pack 9)	9 tabs
Rizatriptan	Maxalt Maxalt MLT	30 mg	5 mg tab 10 mg tab (blister pack 6, 12)	12 tabs

Generic	Brand	Max Daily Dose	Dosage Form	Quantity Limit Per Month
Sumatriptan tablets	Imitrex & generics	200 mg	25 mg tab, 50 mg tab, 100 mg tab (blister pack 9)	9 tablets
Sumatriptan nasal spray	Imitrex & generics	40 mg	5 mg, 10 mg (box of 6)	18 spray units
Sumatriptan nasal powder	Onzetra Xsail	44 mg	22 mg (11 mg in each nostril)	6 nosepieces
Sumatriptan injectable	Imitrex & generics	12 mg	6 mg/0.5 mL	6 vials
Sumatriptan injectable	Sumavel	12 mg	6 mg/0.5 mL units (package of 6)	6 jet injectors
Sumatriptan injectable	Zembrace Symtouch	12 mg	3 mg/0.5 mL (package of 4)	12 auto-injectors
Sumatriptan /naproxen	Treximet	170/1000 mg (2 tablets)	85/500 mg tab (box of 9)	9 tablets
Zolmitriptan	Zomig Zomig ZMT	10 mg	2.5 mg tab (blister pack, 6)	6 tabs
Zolmitriptan nasal spray	Zomig NS	10 mg	5 mg (box of 6)	3 packages (18 spray units)

Abbreviations: d = days; MR = may repeat; NS = nasal spray; PO = orally

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Does the patient have a diagnosis of migraine headaches?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is requested drug a preferred product?	**Yes:** Go to #5	**No:** Go to #4

Approval Criteria		
4. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA within recommended dose limits. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class and dose limits.	**No:** Go to #5
5. Is request for a higher dose than listed in quantity limit chart?	**Yes:** Pass to RPh. Deny; medical appropriateness. • May recommend use of migraine prophylactic therapy and reinforce that doses above those recommended by the manufacturer increase the incidence of medication overuse headache. • One lifetime 90-day taper may be approved at pharmacist's discretion. • Document.	**No:** Trouble-shoot claim payment (e.g., days' supply?). Go to #6.
6. Is the request for two different oral triptans concurrently?	**Yes:** Go to #7	**No:** Approve for 6 months
7. Is this a switch in Triptan therapy due to intolerance, allergy or ineffectiveness?	**Yes:** Document reason for switch and override for concurrent use for 30 days.	**No:** Pass to RPh. Deny; medical appropriateness.

P&T Review: *5/19 (KS); 3/16; 3/10; 9/09; 11/03; 5/03*
Implementation: *5/1/16, 3/23/10; 1/1/10; 7/1/06; 5/31/05; 6/30/04*

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OHSU Drug Effectiveness Review Project Summary Report – CGRP Inhibitors

Date of Review: May 2019 **End Date of Literature Search:** July 31, 2018

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

Research Questions:
1. What is the efficacy and effectiveness of calcitonin gene-related peptide (CGRP) inhibitors for preventative treatment of episodic or chronic migraines based on important outcomes (e.g., headache frequency or reduction in number of migraines per month) compared to placebo or other treatments?
2. What adverse events are associated with CGRP inhibitors in the preventative treatment of migraines (e.g., withdrawals due to adverse events or severe adverse events)?
3. Are there certain sub-populations (based on age, gender, ethnicity, or comorbidities) in which certain CGRP inhibitors are more effective or cause less harm for migraine preventative treatment?

Conclusions:
- No additional high-quality evidence for this review was identified outside the Drug Effectiveness Review Project (DERP) Summary Report.
- Moderate quality evidence from 3 randomized controlled trials (RCTs) of erenumab and fremanezumab compared to placebo showed a statistically significant decrease in migraine days per month for chronic migraine at 12 weeks (-1.7 days to -2.5 days across 3 RCTs).
- Moderate quality evidence from 9 randomized controlled trials of erenumab, fremanezumab, and galcanezumab compared to placebo showed a statistically significant decrease in migraine days per month for episodic migraine at 12 weeks (-0.9 days to -2.8 days across 9 RCTs).
- Low quality evidence from one randomized controlled trial of eptinezumab compared to placebo showed no statistically significant decrease in migraine days per month at 12 weeks.
- There is inadequate evidence to assess the relative efficacy and safety between different CGRP inhibitors or other treatments.
- There is insufficient evidence regarding the long-term safety of CGRP inhibitors beyond 12 to 24 weeks.
- There is insufficient evidence to determine if there is a difference in various subgroup populations in efficacy or safety for eptinezumab, erenumab, fremanezumab, and galcanezumab.

Recommendations:
- No new evidence in the DERP report suggests changes should be made to the preferred drug list (PDL) based on clinical differences between agents.
- No further review or research needed at this time. Review comparative drug costs in the executive session.

Author: David Engen, PharmD

Summary of Prior Reviews and Current Policy

- In September 2018, a new class was created for the preventative treatment of chronic and episodic migraines called CGRP antagonists. Erenumab was the first agent evaluated and prior authorization (PA) criteria was implemented. The review found insufficient evidence to compare the safety and efficacy of erenumab to any other U.S. Food and Drug Administration (FDA)-approved prophylaxis agents. Two additional agents, fremanezumab and galcanezumab, have been recently FDA-approved and added to the CGRP antagonist class since the initial review (see **Appendix 1**). One additional agent, eptinezumab, is still under FDA review. There were 7 total claims for CGRP antagonists in first quarter (November 2018 – January 2019) for the Oregon Medicaid Fee-For-Service (FFS) population.
- There are currently no preferred agents within the CGRP antagonist class. PA approval criteria requires documentation of 4 or more migraine days per month, failure of FDA-approved migraine prophylaxis agents from select classes (beta-blockers, anticonvulsants, and tricyclic antidepressants), and specialist consult prescribing (see **Appendix 2**).

Methods:

The October 2018 drug class report on Calcitonin Gene-Related Peptide Inhibitors for Migraine Prophylaxis by the DERP at the Center for Evidence Based Policy at Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class.

The original report is available to Oregon Pharmacy and Therapeutics Committee members upon request.

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

Summary Findings:

CGRP Inhibitors are human monoclonal antibodies designed to bind to and block CGRP receptor function.[1] It is theorized that migraine headaches may be prevented via inhibition of CGRP-induced vasodilation.[1] The FDA has approved 3 drugs in this class (erenumab, fremanezumab, and galcanezumab) and one additional drug (eptinezumab) is in development and expected to be approved in 2019 (see **Table 1**).[1]

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

Generic Name	Brand Name	Drug Sponsor	Dose(s)	Form	Frequency	FDA Approval Date
erenumab	Aimovig	Amgen	70 mg, 140 mg	Subcutaneous injection	Monthly	May 17, 2018
fremanezumab	Ajovy	Teva	225 mg, 675 mg, 900 mg	Subcutaneous injection	Monthly or every 3 months	September 14, 2018
galcanezumab	Emgality	Eli Lilly	120 mg (after initial 240 mg load)	Subcutaneous injection	Monthly	September 27, 2018
eptinezumab	N/A	Alder	100 mg, 300 mg	Intravenous infusion	Every 3 months	*Anticipated 2019*

An analysis of the comparative efficacy and safety of the CGRP antagonists in migraine prevention treatment was completed by DERP in October 2018.[1] A search ending in July 2018 identified thirteen randomized, placebo-controlled trials and 2 systematic reviews eligible for inclusion. [1] Narrative reviews and studies not published in English were excluded. [1] The methodological quality of all 13 manufacturer-funded studies were rated as fair due to risk of bias from widespread

manufacturer participation in the study design, protocol, analysis, and synthesis of the document. [1] The DERP review evaluated evidence for the CGRP inhibitors based on effectiveness for chronic migraine prophylaxis, episodic migraine prophylaxis, safety, and use in special populations. [1]

Three studies were identified with evidence for erenumab and fremanezumab use in chronic migraine preventative treatment. [1] Chronic migraine was defined as 15 or more days of headaches per month, for at least 3 months, and with migraine features at least 8 days per month. [1] Ten studies were found with evidence for eptinezumab, erenumab, fremanezumab, and galcanezumab use in episodic migraine prophylaxis. [1] Episodic migraine was defined as any migraine not considered chronic which typically included 4 to 14 migraine days per month. [1] The primary effectiveness outcomes addressed in the studies were changes in migraine or headache events per month from baseline. [1] Medication use days, functional ability, quality of life, adverse events, and withdrawals/discontinuations due to adverse events were mostly reported as secondary outcomes of interest. [1] Many of the secondary outcome measures were based on scores from assessment scales where clinical significance of the treatment effect was difficult to establish. [1]

The CGRP inhibitor DERP summary report did not provide any direct comparative efficacy between eptinezumab, erenumab, fremanezumab, and galcanezumab.[1] An ICER network meta-analysis conducted from studies for common drugs used in preventative therapies for chronic and episodic migraine was included in the report. [1] However, since the network meta-analysis is comprised of indirect comparisons, the summary of this DERP report will focus only on direct evidence of CGRP inhibitors in clinical trials. A systematic review by the Canadian Agency for Drugs and Technologies in Health (CADTH) on monoclonal antibodies in migraine prevention was identified, but will not be addressed in this summary due to its poor methodological quality as reported by the DERP authors. [1] Long-term safety outcomes were not reported for any of the CGRP inhibitors. [1] Fifteen unpublished studies were identified that may provide additional efficacy evidence of up to 24 weeks and safety data up to 1.5 years. [1]

The overall treatment effect magnitude for CGRP inhibitors was minimal as most studies reported an average reduction of 0.9 to 2.8 in migraine days compared to placebo. [1] Slightly larger treatment effects were noted among participants with chronic migraine compared to episodic migraine. [1] The clinical significance of the treatment effect size was unclear. [1]

CGRP Inhibitors for Chronic Migraine Prophylaxis

For chronic migraine prophylaxis, there was moderate quality evidence that select CGRP inhibitors were effective in reduction of migraine days, headache hours, and headache days per month. [1] Overall compared to placebo, erenumab and fremanezumab resulted in a statistically significant decrease in migraine days per month at 12 weeks; the difference from a placebo ranged from -1.7 days to -2.5 days across 3 randomized controlled trials (RCTs). [1] Trial summaries for the individual drugs and their primary outcome measures are presented below.

Erenumab

One multicenter, fair quality, phase 2 study (N=667) evaluated erenumab 70 mg and 140 mg versus placebo over 12 weeks. [1] The study enrolled adults between 18 and 65 years of age with a history of chronic migraine in the previous 3 months and during the 4-week run in phase. [1] Concurrent migraine prevention drugs were prohibited in 2 months prior to run-in and during the treatment phase. [1] Acute migraine treatment medications were allowed throughout the study. [1] The primary study endpoint of mean change in migraine days per month from baseline were similar for both active treatment groups (-2.5 [95% CI, -3.5 to -1.4]) compared to the placebo group. [1]

Fremanezumab

Two studies rated as fair methodological quality evaluated fremanezumab at varying doses and frequencies versus placebo.[1] One multicenter, U.S.-based, phase 2b RCT (N= 264) compared monthly doses of fremanezumab 225 mg and 900 mg versus placebo.[1] A separate phase 3 RCT (N=1,130) conducted in North America and Europe compared fremanezumab 225 mg monthly and 675 mg quarterly to placebo.[1] Patient demographics were similar for both studies consisting of at least 85% females with a mean age of roughly 40 years old.[1] Both studies used 12-weeks of active treatment and allowed up to 2 preventative migraine drugs or devices if use was stable for 2 months prior to 4-week run-in period.[1] The phase 2b study reported statistically significant decreases for primary efficacy endpoints in headache hours per month from baseline for fremanezumab versus placebo [225 mg: -22.7 (-44.3 to -1.2); 900 mg: -30.4 (-51.9 to -9.0)].[1] The phase 3 study also reported statistically significant decreases for its primary efficacy endpoint of headache days per month from baseline for active drug versus placebo [225 mg: -2.1 $\pm$ 0.3 ($P < .001$); 675 mg: -1.8 ($P < .001$)].[1,2]

CGRP Inhibitors for Episodic Migraine Prophylaxis

For episodic migraine, there was moderate quality evidence that, compared to placebo, erenumab, fremanezumab, and galcanezumab resulted in a statistically significant decrease in migraine days per month at 12 weeks and up to 24 weeks in some studies; the difference from a placebo ranged from -0.9 to -2.8 days per month across 9 RCTs.[1] There was low quality evidence from one RCT that, compared to placebo, eptinezumab resulted in no statistically significant difference in migraine days per month at 12 weeks.[1] Trial summaries for the individual drugs and their primary outcome measures are presented below.

Erenumab

Two phase 3 RCTs (N=577; N=955) and 1 phase 2 RCT (N=267) evaluated erenumab at 70 mg and 140 mg monthly doses versus placebo.[1] All studies were conducted in multiple study sites in North America and Europe with a 4-week run-in phase and a 12-week or 24-week double-blind active treatment phase.[1] Both phase 3 trials allowed concomitant use of one preventative migraine treatment if the therapy was stable prior to enrollment in the study.[1] Each of the 3 studies reported statistically significant decreases in the primary efficacy endpoint (mean change in monthly migraine days from baseline) for active drug compared to placebo (-1.0 to -1.4 days for 70-mg and -1.9 days (95% CI, -2.3 to -1.4) for 140-mg).[1] Study authors reported many secondary outcomes with regards to changes in quality of life scales which yielded mixed results and variable statistical significance.[1]

Fremanezumab

One phase 2b RCT (N=297) and one phase 3, RCT (N=875) evaluated fremanezumab 225 mg and 675 mg versus placebo.[1] All doses were administered monthly except for the phase 3 trial which evaluated fremanezumab 675 mg quarterly.[1] Both studies were conducted at multiple sites in 9 countries with a 4-week run-in phase and 12-week double-blind active treatment phase.[1] Participants in both studies allowed concomitant use of one migraine preventive treatment if use was stable prior to enrollment.[1] Both studies reported statistically significant decreases in the primary efficacy endpoint (mean change in monthly migraine days from baseline).[1] The mean difference from the placebo ranged from -1.3 days to -2.8 days across doses.[1]

Galcanezumab

Four double-blind studies evaluated galcanezumab versus placebo.[1] One phase 2 RCT (N=218) and one phase 2b RCT (N=274) were conducted at multiple U.S. sites.[1] Two studies were phase 3 RCTs (N=862; N=915) conducted at North American sites, one of which also included Europe, South America, and Asia.[1] In the phase 2 trials, galcanezumab doses ranged from 150 mg to 300 mg every 2 weeks or monthly over 3 months.[1] Both phase 3 trials evaluated galcanezumab 120 mg and 240 mg monthly over 6 months.[1] None of the galcanezumab studies allowed concomitant migraine prophylaxis treatment.[1] The studies used the mean change in monthly migraine days from baseline as the primary efficacy endpoint.[1] Compared to placebo, all 4 studies reported statistically significant decreases in migraine days per month which ranged from -0.9 days to -2.0 days across doses, although one study reported results with a 90% confidence interval.[1]

Eptinezumab

One phase 2 RCT (N=174) evaluated eptinezumab compared to placebo.[1] The study was conducted multiple sites in the U.S. and compared a single 1000 mg intravenous dose of eptinezumab to placebo.[1] No concomitant preventive migraine medication was allowed within 3 months prior to or during the study period.[1] The primary efficacy endpoint was mean change in monthly migraine days from baseline at 5 to 8 weeks.[1] The study authors reported the mean difference compared to placebo to be -1.0 day (95% CI, -2.0 to 0.1) and reported this result as statistically significant (P = .03) using a one-tailed significance test.[1] With data provided in the study, DERP authors calculated the confidence intervals to be -2.0 to 0.04 and the associated P value as 0.06 with a two-tailed t-test.[1] The authors did not observe any significant difference compared to a placebo in monthly migraine days at 12 weeks.[1] The imprecise estimates and small study size limited the author's ability to evaluate efficacy outcomes.[1]

CGRP Inhibitor Safety

Serious adverse events, discontinuations due to adverse events, and all-cause adverse event frequency in active treatment groups were similar in frequency compared to placebo at 12 to 24 weeks across all drugs and doses.[1] Treatment-related liver injury was uncommon and was similar between active treatment and placebo groups.[1] However, the evidence for adverse event outcomes was rated as very low quality for all drugs because of study limitations from the risk of bias due to manufacturer involvement and very serious concerns for imprecision.[1] Long-term safety data for the CGRP inhibitors beyond 24 weeks were not available for evaluation.[1]

CGRP Inhibitor Safety and Effectiveness in Sub-populations

There were few CGRP inhibitor studies that reported findings among sub-populations except for fremanezumab which no reported differences in safety and efficacy among participants with or without concomitant preventative medication.[1] Patients with clinically significant psychiatric or medical conditions including pregnancy were excluded in most studies.[1] Most studies failed to report race and ethnicity information.[1]

References:

1. Kahwati LC, Gartlehner G, Clark R, Patel S, Lazur B, Harrod C. Calcitonin gene-related peptide inhibitors for migraine prophylaxis: a systematic review. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2018.
2. Silberstein SD, Dodick DW, Bigal ME, et al. Fremanezumab for the preventive treatment of chronic migraine. *N Engl J Med.* 2017;377(22):2113-2122. doi: https://dx.doi.org/10.1056/NEJMoa1709038.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form
erenumab-aooe	AIMOVIG AUTOINJECTOR	AUTO INJCT
erenumab-aooe	AIMOVIG AUTOINJECTOR (2 PACK)	AUTO INJCT
fremanezumab-vfrm	AJOVY	SYRINGE
galcanezumab-gnlm	EMGALITY	PEN INJCTR

Calcitonin Gene-Related Peptide (CGRP) antagonists

Goal(s):
- Promote safe use of CGRP inhibitors in adult patients
- Promote use that is consistent with medical evidence and product labeling

Length of Authorization:
- Initial: Up to 3 months
- Renewal: Up to 12 months

Requires PA:
- All calcitonin gene-related peptide (CGRP) antagonists

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA-approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Is this a request for renewal of a previously approved Fee-For-Service prior authorization of a CGRP antagonist for management of migraine headache?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #5

Approval Criteria		
5. Is there documentation that the patient has experienced 4 or more migraine days in the previous month?	**Yes:** Document migraine days per month _____ Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Do chart notes indicate headaches are due to medication overuse?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #7
7. Has the patient failed an adequate trial (≥6 weeks with a documented adherence of ≥80%) of an FDA-approved migraine prophylaxis medication from each of the following classes: beta-blockers, anticonvulsants, and tricyclic antidepressants? OR Does the patient have a documented intolerance, FDA-labeled contraindication, or hypersensitivity to each of the above migraine prophylaxis classes?	**Yes:** Document agents used and dates _____ _____ Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Has the patient received an injection with botulinum toxin for headache treatment once in the previous 2 months?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #9
9. Is the medication being prescribed by or in consultation with a neurologist or headache specialist?	**Yes:** Approve for 3 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Do chart notes indicate headaches are due to medication overuse?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #2

2. Has the patient experienced a documented positive response to therapy, as demonstrated by a reduction in migraine headache frequency and/or intensity from baseline?	**Yes:** Document response Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 5/2019; 9/2018 (DE)
Implementation: 11/1/2018

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Drug Class Update with New Drug Evaluation: Potassium Exchangers

Date of Review: May 2019
Generic Name: Sodium Zirconium Cyclosilicate

End Date of Literature Search: 03/04/2019
Brand Name (Manufacturer): Lokelma™ (AstraZeneca)
Dossier Received: yes

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

Purpose for Class Update:
Review new published data for management of hyperkalemia to help inform whether current Oregon Health Plan (OHP) policies remain appropriate for access to these medications. Review evidence for a new potassium binder, sodium zirconium cyclosilicate (SZC), recently approved by the United States (U.S.) Food and Drug Administration (FDA) for treatment of hyperkalemia in adults.

Research Questions:
1. Is there new evidence for differences in efficacy or harms between drug therapies (patiromer and sodium polystyrene sulfonate) used to treat hyperkalemia in adults?
2. What is the evidence for the safety and efficacy for SZC in treating hyperkalemia in adults?
3. Are there subgroups of patients based on demographics (e.g., age, racial groups, gender), comorbidities (e.g., drug-disease interactions, impaired renal function), or other medications (drug-drug interactions) for which SZC is more effective or safe?

Conclusions:
Comparative Evidence for Potassium Exchangers
- Two moderate quality systematic reviews evaluated published data regarding the safety and efficacy of patiromer and SZC in treating hyperkalemia.[1,2] One systematic review summarized case reports of gastrointestinal events associated with the use of sodium polystyrene sulfonate (SPS).[3]
- The efficacy and safety of patiromer in hyperkalemic patients with heart failure or chronic kidney disease (CKD) was assessed in a 2018 systematic review and meta-analysis including 3 moderate quality studies.[1] There was a no statistically significant difference in all-cause mortality and serious cardiovascular events with patiromer compared to placebo (Risk Ratio (RR) 0.31; 95% CI 0.03 to 2.90; p=0.30 and RR 3.5; 95% CI 0.40 to 30.27; p=0.26; respectively).[1] Patiromer lowered serum potassium concentrations more than placebo, and more patients developed hyperkalemia with placebo.[1]
- A systematic review that compared efficacy and safety of patiromer and SZC in the treatment of hyperkalemia was published in 2017.[2] The meta-analysis of 3 moderate quality trials for patiromer showed a significant 0.70 mEq/L (95% confidence interval [CI] 0.48 to 0.91 mEq/L) change in serum potassium at 4 weeks.[2] The meta-analysis of low quality data from 3 SZC trials found a significant change in potassium at 48 hours, of 0.67 mEq/L (95% CI 0.45 to 0.89

mEq/L).[2] Analysis of pooled adverse effects from these trials indicates that patiromer was associated with more gastrointestinal upset and electrolyte depletion (hypomagnesemia), whereas SZC was associated more frequently with edema.[2]

- A 2013 systematic review evaluated case reports of gastrointestinal events associated with the use of SPS.[3] The literature search identified 58 cases of adverse events related to SPS administration.[3] The presenting gastrointestinal symptoms were abdominal pain and distension (n=33), gastrointestinal bleeding (n=13), diarrhea (n=10), and nausea and vomiting (n=6).[3] Mortality was reported in 33% of these cases due to gastrointestinal injury.[3]

New Drug Evaluation: Sodium Zirconium Cyclosilicate

- The safety and efficacy of SZC in hyperkalemic outpatients was evaluated in two phase 3, randomized, double-blind, placebo-controlled trials of similar design.[4,5]
- In Study 1 (ZS-003), patients with hyperkalemia who received SZC had a significant reduction in potassium levels at 48 hours compared with patients who received placebo, with normokalemia maintained during 12 days of maintenance therapy.[4]
- In the HARMONIZE trial, open-label SZC reduced serum potassium to normal levels within 48 hours in outpatients with hyperkalemia.[5] Compared with placebo, 3 doses of SZC (5 gram, 10 grams and 15 grams) resulted in lower potassium levels and a higher proportion of patients with normal potassium levels for up to 28 days.[5] In the randomized phase, serum potassium was significantly lower during days 8-29 with all 3 zirconium cyclosilicate doses versus placebo (4.8 mEq/L [95% CI, 4.6-4.9], 4.5 mEq/L [95% CI, 4.4-4.6], and 4.4 mEq/L [95% CI, 4.3-4.5] for 5 g, 10 g, and 15 g; 5.1 mEq/L [95% CI, 5.0-5.2] for placebo; $P < 0.001$ for all comparisons).[5]
- In both phase 3 clinical trials, SZC was well-tolerated and the incidence of adverse events was comparable between the active-treatment and placebo groups.[4,5] In the HARMONIZE trial, SZC increased the incidence of edema in a dose-dependent manner (2%, 6%, and 14% for 5 gram, 10 gram, and 15 gram SZC doses versus 2% with placebo).[5] Hypokalemia developed in 10% and 11% of the patients in the 10 gram and 15 gram SZC groups, versus none in the 5 gram or placebo groups.[5] The hypokalemia resolved with dosage reduction or discontinuation of SZC.[6]
- There is insufficient evidence to evaluate the efficacy and safety of zirconium cyclosilicate beyond 4 weeks and to assess long-term clinical outcomes. Some patient groups that may benefit from potassium-lowering treatments, such as those receiving dialysis or hospitalized patients, were excluded from both trials.

Recommendations:

- Add sodium zirconium cyclosilicate to patiromer PA criteria it insure appropriate utilization for FDA-approved indications.
- Evaluate comparative costs in executive session to determine Preferred Drug List (PDL) status for all 3 potassium exchangers; patiromer, SPS, and SZC.

Summary of Prior Reviews and Current Policy

A new potassium binder, patiromer, was reviewed at the May 2016 Pharmacy and Therapeutics (P and T) Committee meeting. Low quality evidence demonstrates patiromer can decrease serum potassium levels from 0.35 mEq/L to 1.23mEq/L over 4 weeks of therapy in hyperkalemic patients with chronic kidney disease (CKD) on a renin angiotensin aldosterone system (RAAS) inhibitor. There is low quality evidence that in patients with CKD on a RAAS inhibitor with baseline hyperkalemia, patiromer is associated in a reduction in the recurrence of hyperkalemia (60% vs. 15%) through 8 weeks of treatment. The trials were short term and not designed to detect differences in any long term complications of chronic hyperkalemia (sudden cardiac death or ventricular arrhythmias).There is insufficient evidence that patiromer prevents long term complications, including arrhythmias. Due to the slow onset of patiromer, it is not recommended to be used in the acute treatment of hyperkalemia (potassium ≥ 6.5 mEq/L).[7] The phase 3 patiromer trials were short-term and not designed to detect differences in any long-term complications of chronic hyperkalemia (i.e., sudden cardiac death or ventricular arrhythmias). The recommendations were to defer Preferred Drug List (PDL) decisions until a review

of sodium polystyrene sulfonate and SZC (which was awaiting FDA approval) could be presented at a future P and T meeting. Clinical PA criteria for patiromer were implemented to prevent its use in the emergent setting or in scenarios not supported by the medical literature.

Background:
Hyperkalemia is a potentially life-threatening metabolic disorder caused by inability of the kidneys to excrete potassium, impairment of the mechanisms that move potassium from the circulation into cells, or excessive production through oral intake.[8] Potassium is primarily absorbed form the gastrointestinal tract via the small intestine and the kidneys regulate potassium excretion and reabsorption.[9] Hyperkalemia is defined as a serum potassium concentration greater than 5.0 mEq per liter.[10] While the definitions of mild, moderate, and severe hyperkalemia vary, severe hyperkalemia is most often defined as a serum potassium concentration greater than 6.5 mEq per liter or the presence of electrocardiographic changes resulting from an abnormal serum potassium concentration.[10] Hyperkalemia is most often associated with impaired renal function, hyperglycemia, cell lysis (rhabdomyolysis or hemolysis) or acidosis. Medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), cyclosporine, tacrolimus, eplerenone, spironolactone, angiotensin converting enzyme inhibitors (ACEIs) and angiotensin-II receptor blockers (ARBs) can cause hyperkalemia due to interference with the renin-angiotensin-aldosterone pathway. Other medications that can cause hyperkalemia include: azole antifungals, triamterene, amiloride, trimethoprim, digoxin, and beta blockers.[11] Hyperkalemia may lead to altered mental status, muscle weakness, paralysis, impaired renal acidification, or cardiac arrhythmias with fatal outcomes.[11]

The incidence and prevalence of hyperkalemia in the general population is low (2–3%).[12] However, studies in patients with CKD have found higher frequencies of hyperkalemia, often as high as 40–50%, especially in diabetic patients, those with advanced stages of CKD, and heart failure patients treated with RAAS inhibitors.[12] Therapy for CKD and heart failure often includes RAAS inhibitors, and the administration of these medications may lead to increases in plasma potassium.[13] Hyperkalemia has been reported to occur in approximately 10% of outpatients within a year of initiating an ACE inhibitor or ARB.[14] Consequently, hyperkalemia may often lead to dose reduction or discontinuation of RAAS therapy, which in turn may lead to worsening of CKD or heart failure.

Acute management of hyperkalemia involves various interventions, including the intravenous administration of drugs that affect the cellular distribution of potassium and drugs that stabilize the myocardium, or definitive measures to remove potassium from the body.[12] Hemodialysis is an effective acute therapy for potassium removal from the body in an inpatient setting, but it is invasive and requires specialized equipment and personnel.[12] Medications used to manage acute hyperkalemia are described in **Table 1**.

Table 1. Medications for Treating Acute Hyperkalemia[8,10]

Agent	Mechanism	Risks/Considerations
Intravenous insulin 10 units co-administered with intravenous dextrose (50%) 25 grams	Stimulates potassium uptake into cells	• Does not permanently remove potassium from body • Risk for hypoglycemia and electrolyte imbalances
Beta-adrenergic agonist (e.g., nebulized albuterol 10 -20 mg in 4 ml normal saline over 15 minutes)	Stimulates potassium uptake into cells	• Does not permanently remove potassium from body • Can precipitate tachycardia • Inconsistent response • May not be appropriate for use in patients with hypertension, heart failure, or tachyarrhythmia
Intravenous calcium gluconate (10%) or calcium chloride (10%) – 1 gram over 10 minutes	Protects against negative cardiac effects of potassium imbalance	• Does not affect potassium levels • Hypercalcemia • Can precipitate bradycardia and other arrhythmias

		• Can cause tissue damage • Contraindicated in patients taking digoxin

Abbreviations: mg = milligram; ml = milliliters

Chronic management of hyperkalemia usually starts by identifying and eliminating correctable causes, such as a high potassium intake, hyperkalemia-inducing medications or metabolic acidosis.[12] Effective interventions include dietary education and a review of prescribed, over-the-counter and herbal medications.[12] In addition, loop diuretics and sodium bicarbonate can be administered.[12] Administration of aldosterone (in the form of oral fludrocortisone acetate) is effective in patients with aldosterone deficiency, but high doses might be needed, which can induce sodium retention, edema and hypertension.[12] Potassium binding resins such as SPS and patiromer are other therapeutic options.[12] Due to their delayed onset of action, SPS and patiromer should not be used as an emergency treatment for life-threatening hyperkalemia.[7,15] **Table 2** provides an overview of the 3 FDA-approved potassium exchangers currently on the U.S. market.

Sodium polystyrene sulfonate binds potassium in the intestine and increases fecal potassium excretion, thereby reducing serum potassium concentrations. The FDA first approved SPS for the treatment of hyperkalemia in 1958, 4 years before passage of the Kefauver-Harris Drug Amendments, which require drug manufacturers to prove the effectiveness of their products before marketing them.[16] No data from clinical trials of SPS are included in the SPS prescribing information.[15] Sodium polystyrene sulfonate was studied in one small (n=33), short term (7 day), randomized controlled trial which demonstrated limited efficacy of SPS compared to placebo.[17] In this study, patients with CKD and mild hyperkalemia (5.0 to 5.9 mEq/L) received either SPS 30 grams once daily or placebo. Although SPS was superior to placebo in the reduction of serum potassium (mean difference between groups, -1.04 mEq/L; 95% CI: -1.37 to -0.71), achieving normokalemia at the end of treatment was not statistically significantly different between treatment groups (73% SPS vs. 38% placebo, P=0.07).[17] In 2009, the FDA issued a black box warning against the concomitant use of SPS and sorbitol due to the potential for dangerous GI side effects, including intestinal necrosis, bleeding, and ischemic colitis.[15] Additional limitations of SPS use indicated in the prescribing information include risk of hypokalemia, hypernatremia, diarrhea, and gastrointestinal intolerance.[15]

Patiromer, a non-absorbed, potassium-binding polymer, exchanges calcium for potassium in the distal colon which promotes fecal potassium excretion.[7] Patiromer binds to other orally administered medicines including ciprofloxacin, levothyroxine, and metformin. Therefore, administration of patiromer is recommended at least 6 hours before or after other oral medications.[7] In clinical trials, hypomagnesemia was reported as an adverse reaction in 5.3% of patients treated with patiromer.[7] The most common adverse event was constipation that led to patiromer discontinuation in 6–9% of patients.[7] Patients are advised to avoid patiromer use if they have severe constipation, bowel obstruction, or impaction.[7] Additionally, patiromer should be stored in the refrigerator at 2° to 8°C.[7]

Table 2. Medications FDA-Approved to Treat Non-Life-Threatening Hyperkalemia[6,7,15]

Characteristic	Sodium Polystyrene Sulfonate	Patiromer	Sodium Zirconium Cyclosilicate
Brand Name	Kayexalate®	Veltassa®	Lokelma™
Year of FDA approval	1958	2015	2018
Site of Action	Colon	Colon	Entire gastrointestinal tract
Mechanism of Action	Exchanges potassium for sodium	Exchanges potassium for calcium	Exchanges potassium for sodium
Sodium Content	1.5 grams sodium per 15 gram dose	No sodium content	400 mg sodium per 5 gram dose
Sorbitol Content	20 grams sorbitol per 15 gram dose	4 grams sorbitol per 8.4 gram dose	No sorbitol content
Dose	Oral: 15 to 60 grams up to 4 times a day Rectal: 30 to 50 grams every 6 hours	Oral: 8.4 grams once a day with food, can be advanced up to 16.8 to 25.2 grams at weekly intervals	Oral: 10 grams three times a day for 48 hours followed by 10 grams once a day with food
Onset of Effect	2 to 6 hours	7 hours	1 hour

How Supplied	Light brown finely ground bulk powder	8.4, 16.8, and 2.5 2 gram packets	5 and 10 gram packets
Storage	Room temperature	Refrigerate; use within 3 months upon removal from refrigerator	Room temperature
Drug Interactions	Binds significantly to warfarin, metoprolol, phenytoin, furosemide, amlodipine, and amoxicillin. Administer at least 3 hours before or 3 hours after other oral medications.	May bind to orally administered medications and reduce their effectiveness; separate administration by 6 hours.	May increase concentrations of weakly acidic drugs such as furosemide and atorvastatin. May decrease the concentrations of weakly basic drugs such as dabigatran.
Safety Concerns	Colonic necrosis (case reports)	Hypomagnesemia (5.3%)	Edema 8-11% (dose dependent)

Methods:

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

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

Systematic Reviews:

Efficacy and Safety of Patiromer in Hyperkalemia

The efficacy and safety of patiromer in hyperkalemic patients with heart failure or CKD was evaluated in a 2018 moderate quality systematic review and meta-analysis.[1] The literature search was conducted through 2015. Three moderate quality studies were included in the meta-analysis. Primary outcomes included: all-cause mortality, reduction in hospitalization, episodes of hypokalemia or hyperkalemia, and cardiovascular and gastrointestinal adverse events during the treatment period. There was a no statistically significant difference in all-cause mortality and serious cardiovascular events with patiromer compared to placebo (RR 0.31; 95% CI 0.03 to 2.90; p=0.30 and RR 3.5; 95% CI 0.40 to 30.27; p=0.26; respectively).[1] Hospitalization data were unavailable. Although serious gastrointestinal events were more common with placebo, there was a significant reduction (P=0.02) in the risk of non-serious gastrointestinal events with placebo (risk ratio=7.23; 95% CI 1.35 to 38.71).[1] Patiromer lowered serum potassium concentrations more than placebo, and more patients developed hyperkalemia with placebo.[1] The authors concluded that although patiromer seems promising in terms of efficacy and safety in multiple clinical trials, more RCTs with active comparator or existing standard of care in patients with established hyperkalemia are essential to come to a consensus about the indication and proper use of patiromer.[1]

Systematic Review and Meta-Analysis of Patiromer and Sodium Zirconium Cyclosilicate

A moderate quality systematic review designed to compare efficacy and safety of patiromer and SZC in the treatment of hyperkalemia was published in 2017.[2] Significant heterogeneity was found in the meta-analysis with an I^2 value ranging from 80.6–99.6%.[2] The meta-analysis of 3 moderate quality trials for patiromer

showed a significant 0.70 mEq/L (95% confidence interval [CI] 0.48 to 0.91 mEq/L) change in serum potassium at 4 weeks compared to baseline.[2] The meta-analysis of low quality data (due to the open label design of the initial run-in phase) from 3 SZC trials found a significant change in potassium at 48 hours, of 0.67 mEq/L (95% CI 0.45 to 0.89 mEq/L).[2] By 1 hour after SZC administration, change in potassium was 0.17 mEq/L (95% CI 0.05 to 0.30).[2] Analysis of pooled adverse effects from these trials indicates that patiromer was associated with more gastrointestinal upset (7.6% constipation, 4.5% diarrhea) and electrolyte depletion (7.1% hypomagnesemia), whereas SZC was associated with edema (0.9%).[2] Both agents exhibited statistically and clinically significant reductions in potassium for the primary end point of this meta-analysis.[2]

Safety of Sodium Polystyrene Sulfonate

A 2013 systematic review evaluated case reports of gastrointestinal events associated with the use of SPS.[3] The literature search identified 58 cases of adverse events related to SPS administration.[3] The presenting gastrointestinal symptoms were abdominal pain and distension (n=33), gastrointestinal bleeding (n=13), diarrhea (n=10), and nausea and vomiting (n=6).[3] The median time from the first sodium polystyrene sulfonate dose to the presentation of gastrointestinal symptoms was 2 days (interquartile range, 1-5 days).[3] The colon was the most commonly affected segment of the gastrointestinal tract (n=44) followed by the small intestine (n=12).[3] Histopathologic findings associated with SPS use were necrosis of the bowel wall (n=36), ulceration (n=28), and perforation (n=5).[3] All patients had histopathologic examination of affected gastrointestinal segments, which demonstrated SPS crystals in 90% of patients.[3] For patients with gastrointestinal injury associated with SPS use, the overall mortality rate was 33%.[3] Ninety-four percent of patients who died had colonic necrosis on biopsy.[3] The authors conclude SPS use, both with and without sorbitol, may be associated with fatal gastrointestinal injury.[3] The prescribing information for SPS has been modified to include warnings about serious gastrointestinal events (bleeding, ischemic colitis, perforation) associated with SPS administration.[15] Use of SPS should be avoided in patients at risk for developing constipation or impaction (inflammatory bowel disease, vascular intestinal atherosclerosis, previous bowel resection, or bowel obstruction).[15]

After review, one systematic review was 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).[18]

Guidelines: The National Institute for Health and Care Excellence (NICE) is currently in the process of developing guidance documents for the use of patiromer and SZC in treating hyperkalemia. Final publication of both documents is pending.

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

NEW DRUG EVALUATION: Sodium Zirconium Cyclosilicate (Lokelma™)

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:
Sodium zirconium cyclosilicate (SZC) is a non-absorbable compound that exchanges hydrogen and sodium ions for potassium in the gastrointestinal tract.[6] It is FDA-approved to treat non-life threatening hyperkalemia in adults.[6] The SZC new drug application was submitted to the FDA in 2015, but approval was delayed until 2018 due to facility inspection findings, drug-drug interaction liability, and outstanding labeling issues.[19] Sodium zirconium cyclosilicate is supplied in individual powder packets containing 5 or 10 grams which must be reconstituted into an oral solution before administration. For initial treatment of hyperkalemia, the recommended dose is 10 grams administered three times a day for up to 48 hours.[6] For continued treatment, the recommended dose is 10 grams once daily.[6] The dose may be up-titrated based on the serum potassium level at intervals of 1-week or longer and in increments of 5 grams.[6] The recommended maintenance dose ranges from 5 grams every other day to 15 grams once daily.[6] Due to its delayed onset of action, SZC should not be used as emergency treatment for acute hyperkalemia.[6]

The efficacy of SZC in hyperkalemic outpatients was evaluated in two phase 3, randomized, double-blind, placebo-controlled trials of similar design.[4,5] Study 1 (ZS-003) evaluated the effectiveness of SZC in lowering serum potassium in a two-phase, double-blind trial in patients with hyperkalemia (5 to 6.5 mEq/L). In the initial phase, 753 patients were randomized to receive one of four doses of SZC (1.25, 2.5, 5, 10 grams) or placebo, administered three times daily for the initial 48 hours with meals. All concomitant medications were kept constant throughout the study, including diuretic agents, RAAS inhibitors, and antidiabetic therapies. Approximately 67% of subjects were taking RAAS inhibitors.[4] Enrolled subjects had heart failure (40%), CKD (75%) or diabetes (60%) in addition to hyperkalemia.[4] No dietary restrictions were required; patients were instructed to continue their usual diet without any specified changes. Seventy-two percent of patients (n=543) who achieved a potassium level between 3.5 and 5 mEq/L after receiving SZC during the acute phase were re-randomized to receive either their original SZC treatment dose or placebo once daily with breakfast from days 3 to 14.[4] Patients assigned to the placebo group in the initial phase were randomly assigned to receive either SZC 1.25 grams or 2.5 grams in the maintenance phase.[4] Study drug dose adjustment during the study was not permitted.

The primary endpoint in the initial phase was the difference in the exponential rate of change in serum potassium levels during the initial 48 hours of the study, comparing placebo-treated patients versus SZC-treated patients.[4] The investigators felt the exponential rate of change was a more clinically relevant end point than the absolute change from baseline, since it includes the time to onset and incorporates all potassium measurements throughout the initial 48 hours.[4] At 48 hours, the mean exponential rates of change from baseline per hour were reductions of 0.11% in the group receiving SZC 1.25 grams, 0.16% in the group receiving SZC 2.5 grams , 0.21% in the group receiving SZC 5 grams and 0.30% in the group receiving SZC 10 g, as compared with a reduction of 0.09% per hour in the placebo group ($P<0.001$ for the comparison with the three highest-dose groups; $P>0.05$ for the comparison with the 1.25-gram group).[4] The primary endpoint in the maintenance phase was the mean exponential rate of change in the mean serum potassium levels over the 12-day treatment interval, comparing patients receiving SZC versus those receiving placebo.[4] The mean exponential rate of change was an increase of 0.14% per hour in the group receiving SZC 10 grams versus 1.04% per hour in the respective placebo group ($P<0.001$), and an increase of 0.09% per hour with patients receiving SZC 5 grams versus 0.47% per hour with placebo ($P = 0.008$).[4] The mean exponential rate of change with the 1.25 gram and 2.5 gram doses of SZC did not differ significantly from the rates with placebo and specific rates were not reported.[4]

The second trial (HARMONIZE), was a double-blind, two-phase trial evaluating SZC in hyperkalemic outpatients ($K > 5.1$ mEq/L). Baseline characteristics in this trial were similar to Study 1.[5] Two hundred fifty-eight adult patients entered a 48-hour, open-label run-in period during which they received 10 gm of SZC three times daily for a total of 6 doses. A significant change in potassium (−0.2 mEq/L; 95% CI, −0.3 to −0.2; $P<0.001$) was noted 1 hour after the first 10-gm dose compared with baseline.[5] In the initial open-label phase, a mean reduction of −1.1 mEq/L (95% CI: −1.1 to −1.0 mEq/L, $P<0.001$) in serum potassium was noted from baseline to 48 hours; the proportion of patients achieving normokalemia at 48 hours was 98%.[5]

Ninety-two percent of patients achieving normokalemia (3.5-5.0 mEq/L) in the open label phase were then randomized 4:4:4:7 to receive SZC, 5 g (n = 45 patients), 10 g (n = 51), or 15 g (n = 56), or placebo (n = 85) daily for 28 days.[5] Reasons for not entering the maintenance phase included hypokalemia, hyperkalemia, and withdrawal of consent.[5] If a patient's potassium value was between 3.0 and 3.4 mEq/L at any time during the randomized phase, the dose was reduced from once daily to every other day for the remainder of the study.[5] The primary endpoint in the randomized withdrawal phase was the mean serum potassium value during days 8 to 29 in each SZC-treated group versus placebo. In the randomized phase, serum potassium was significantly lower during days 8-29 with all 3 zirconium cyclosilicate doses versus placebo (4.8 mEq/L [95% CI, 4.6-4.9], 4.5 mEq/L [95% CI, 4.4-4.6], and 4.4 mEq/L [95% CI, 4.3-4.5] for 5 g, 10 g, and 15 g; 5.1 mEq/L [95% CI, 5.0-5.2] for placebo; P < .001 for all comparisons).[5] Refer to the comparative evidence table (**Table 5**) for more details about each trial.

Study Limitations:
In the Study 1 (ZS-003), the mean exponential rates of change with the 4 SZC doses were only compared to placebo, not to each other. Study 1 was not appropriately powered to detect the adverse event of hypokalemia. The HARMONIZE trial included an initial open-label, run-in phase which was not double blinded. Both trials were of short duration (12 to 28 days), and clinical outcomes other than potassium levels were not assessed. Some patient groups that may benefit from potassium-lowering treatments, such as those receiving dialysis or hospitalized patients, were excluded from both trials. The dosage of the RAAS inhibitor and duration of time patients had been receiving RAAS inhibitor before study entry were not noted in either trial. Other medications that may have an effect on serum potassium, such as diuretics and aldosterone antagonists, were not assessed. Finally, although the numbers of patients with conditions commonly associated with hyperkalemia were noted, the authors did not state how many patients had more than one of the associated concomitant conditions. Further studies are needed to evaluate the efficacy and safety of zirconium cyclosilicate beyond 4 weeks and to assess long-term clinical outcomes.

Clinical Safety:
In both phase 3 clinical trials, SZC was well-tolerated and the incidence of adverse events was comparable between the active-treatment and placebo groups.[4,5] In the HARMONIZE trial, SZC increased the incidence of edema in a dose-dependent manner (2%, 6%, and 14% for 5 gram, 10 gram, and 15 gram SZC doses versus 2% with placebo).[5] Each 5 gm dose of SZC contains 400 mg of sodium; therefore, edema appears to be related to the sodium load administered. The incidence of edema compiled by the manufacturer from all clinical trials is summarized in **Table 3**.The clinical importance of SZC-inducible sodium retention, particularly in susceptible patients with heart failure or CKD, remains to be determined in ongoing trials. In the HARMONIZE trial, hypokalemia developed in 10% and 11% of the patients in the 10-g and 15-g zirconium cyclosilicate groups, versus none in the 5-g or placebo groups.[5] The hypokalemia resolved with dosage reduction or discontinuation of SZC.[6]

Table 3. Incidence of edema in clinical trials[6]

Adverse Event	Placebo	5 gm	10 gm	15 gm
Edema	2.4%	4.4%	5.9%	16.1%

Sodium zirconium cyclosilicate can temporarily increase gastric pH, which may alter the absorption of co-administered drugs with acid-dependent solubility, such as some azole antifungals and antiretroviral drugs.[6] Therefore, the manufacturer recommends that oral medications with acid dependent solubility should not be taken within 2 hours of SZC.[6]

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

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Serum potassium levels
2) Symptoms related to hyperkalemia: i.e. cardiac arrhythmias
3) Time to serum potassium normalization
4) Adverse event rates
5) Serious adverse events
6) Study withdrawal due to an adverse event

Primary Study Endpoints:

1) Exponential rate of change in potassium levels at 48 hours
2) Mean serum potassium level during the 12 days of treatment
3) Mean serum potassium level during days 8-29 of treatment

Table 4. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Exchanges sodium ions for potassium in the gastrointestinal tract which increases fecal potassium excretion and reduces serum potassium.
Oral Bioavailability	Not absorbed
Distribution and Protein Binding	N/A, not absorbed
Elimination	Fecal
Half-Life	N/A, not absorbed
Metabolism	N/A, not absorbed

Abbreviations: N/A = not available

Table 5. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Packham et al.[4] MC, MP, DB, PC, RCT 2 Phase Trial: Initial Phase over 48 hours followed by Maintenance Phase over 12 days N=753	**Initial Phase (2 days):** 1. SZC 1.25 gm 2. SZC 2.5 gm 3. SZC 5 gm 4. SZC 10 gm 5. Placebo Administered three times a day with meals for 48 hours	Demographics: 1. Mean baseline serum potassium level=5.3 mEq/L 2. Mean age - 65 yo 3. Gender - 60% men 4. Race - 86% Caucasian 5. Percent with eGFR < 60 mL/min - 75% 6. Taking RAASi - 67% 7. Diabetic - 60% 8. Percent with HF - 40%	**Initial Phase:** 1. 154 2. 141 3. 157 4. 143 5. 158 **Maintenance Phase:** ITT: 1. 49 2. 54 3. 65 4. 63 5. 216	Primary Endpoint: Initial Phase: Mean exponential rate of change in the mean serum potassium level from baseline at 48 hours 1. 0.11% per hour 2. 0.16% per hour 3. 0.21% per hour 4. 0.3% per hour 5. 0.09 per hour 1 vs. 5: p>0.05 All other groups vs. 5: p<0.001 Secondary Endpoints: Initial Phase: Mean Serum Potassium at 48 hours	 NS NA	**Initial Phase:** Any AE 1. 16.2% 2. 9.2% 3. 14% 4. 11.9% 5. 10.8% Gastrointestinal Disorder 1. 4.5% 2. 2.1% 3. 3.8% 4. 3.5% 5. 5.1%	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Patients were randomized 1:1:1:1:1 to one of 5 groups in both phases. Baseline demographics similar between groups. Randomization was blinded and conducted by a third party not associated with clinical management of the study. Performance Bias: Low. First 2 doses of SZC in the initial phase were administered at the study site and subsequent doses were administered as an outpatient. Placebo and SZC were identical in appearance. Detection Bias: Low. Potassium levels sent to a central laboratory for analysis and verification.

	Maintenance Phase (12 days): 1. SZC 1.25 gm 2. SZC 2.5 gm 3. SZC 5 gm 4. SZC 10 gm 5. Placebo Administered once daily on days 3 to 14	Key Inclusion Criteria: 1. Adults over 18 years of age with a serum potassium level 5.0 to 6.5 mEq/L with the ability to undergo repeated blood draws Key Exclusion Criteria: 1. Patients on dialysis 2. Insulin-dependent diabetics 3. Subjects with cardiac arrhythmias needing immediate treatment 4. Participation in another clinical trial within 30 days 5. Potassium level > 6.5 mEq/L 6. Subjects with life expectancy of less than 3 months	PP: 1. 48 2. 52 3. 59 4. 61 5. 205 **Maintenance Phase** Attrition: 1. 1% 2. 1% 3. 1% 4. 1% 5. 5%	1. 5.1 mmol/L 2. 4.9 mmol/L 3. 4.8 mmol/L 4. 4.6 mmol/L 5. 5.3 mmol/L MR = -0.25 mmol/L (95% CI -0.32 to -0.19) 1 vs. 5: MR 0.3 mmol/L; NS 2 vs. 5: MR: -0.46 mmol/L (95% CI -0.53 to -0.39) p<0.001 3 vs. 5: MR: -0.54 mmol/L (95% CI -0.62 to -0.47) p<0.001 4 vs. 5: MR: 0.73 mmol/L (95% CI -0.82 to -0.65) p<0.001 Maintenance phase: Mean exponential rate of change in the mean serum potassium level over 12-day treatment interval. 1. NR 2. NR 3. 0.09% per hour 4. 0.14% per hour 5. 0.47% per hour (5 gm comparator) and 1.04% per hour (10 gm comparator group) 1 vs. 5: NS 2 vs. 5: NS 3 vs. 5: P=0.008 4 vs. 5: P<0.001 Mean serum potassium level during the 12-day treatment interval. 1. NR 2. NR 3. 4.7mmol/L 4. 4.5 mmol/L 5. > 5.0 mmol/L 1 or 2 vs. 5: NS 3 or 4 vs. 5: P<0.001	NS NA NA NA NS NS NA NA NS NA	Cardiac Disorder 1. 0.6% 2. 0% 3. 1.9% 4. 1.4% 5. 0% Hypokalemia 1. 0% 2. 0% 3. 0% 4. 0% **Maintenance Phase:** Any AE 1. 25% 2. 22% 3. 22% 4. 33% 5. 25% Gastrointestinal Disorder 1. 4% 2. 6% 3. 7% 4. 5% 5. 4% Cardiac Disorder 1. 0% 2. 0.9% 3. 3.1% 4. 3.2% 5. 0.9% 95% CI and p values NR for all outcomes		Attrition Bias: Low. Attrition rates were similar in all study arms. Reasons for withdrawal were similar across all arms. Reporting Bias: Low. Study protocol available online. All pre-specified primary and secondary outcomes reported. Other Bias: High. ZS Pharma had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Primary author served as a consultant for ZS Pharmacy. One author is an employee of ZS Pharma. Six authors have received grant support from ZS Pharma or served on advisory boards for ZS Pharma. **Applicability**: Patient: Included broad representation of patients in outpatient setting with hyperkalemia. Patients on dialysis, inpatients, or K >6.5 were excluded from this trial, so conclusions about safety or efficacy cannot be drawn in these populations. Intervention: This was a dose finding trial. Comparator: Placebo used as a comparator. Another resin (SPS or patiromer) would have provided reasonable comparative efficacy. Outcomes: Potassium levels are reasonable to assess hyperkalemia. SZC doses only compared to placebo, not to each other. Setting: 65 sites in the United States, Australia and South Africa

2. Kosiborod et al.[5] MC, MP, DB, PC, RCT 2 phases: 258 subjects in the Initial OL Phase. Followed by 237 subjects with potassium level 3.5 to 5.0 randomized to the PC Maintenance Phase N=258	**Initial OL Phase (2 days):** 1.SZC 10 gm three times a day with meals for 48 hours (6 doses) **Maintenance PC Phase (28 days):** 1. SZC 5 gm once daily 2. SZC 10 gm once daily 3. SZC 15 gm once daily 4.Placebo once daily	Demographics: 1. Mean baseline serum potassium level=5.6 meq/L 2. Mean age - 64 yo 3. Gender - 58% men 4. Race - 83% Caucasian 5. Percent with eGFR < 60 ml/min - 66% 6. Taking RAAIs - 70% 7. Diabetic - 66% 8.Percent with HF - 36% Key Inclusion Criteria: 1. Ambulatory patients over 18 yo with a potassium level ≥ 5.1 mEq/L with the ability to have repeated blood draws Key Exclusion Criteria: 1. Pseudohyperkalemia signs and symptoms 2. Subjects treated with lactulose, Xifaxan, or other non-absorbed antibiotics for hyperammonemia within 7 days of enrollment 3. Subjects treated with resins: sevelamer, SPS, calcium acetate, calcium carbonate or lanthanum within 7 days of study enrollment 4. Patients on dialysis or with cardiac arrhythmias 5. Potassium level > 6.5 mEq/L 6. Subjects with life expectancy of less than 3 months	Initial Phase: 1. 258 Maintenance Phase: ITT : 1. 45 2. 51 3. 56 4. 85 PP: 1. 40 2. 44 3. 49 4. 75 Attrition during maintenance phase: 1. 5 (11%) 2. 7 (14%) 3. 7 (13%) 4. 10 (12%)	Primary Endpoint: Mean serum potassium level in each study group during days 8-29 of the randomized phase 1. 4.8 meq/L (95% CI 4.6 to 4.9) 2. 4.5 meq/L (95% CI 4.4 to 4.6) 3. 4.4 meq/L (95% CI 4.3 to 4.5) 4. 5.1 meq/L (95% CI 5.0 to 5.2) 1 vs. 4: MR = 0.3 meq/L; P<0.001 2 vs. 4: MR = 0.6 meq/L; P<0.001 3 vs. 4: MR = 0.7 meq/L; P<0.001 Secondary Endpoints: Proportion of patients who were normokalemic (3.5–5 meq/L) on day 29 1. 71%; p=0.01 vs. 4 2. 76%; p=0.002 vs. 4 3. 85%; p<0.001 vs. 4 4. 48%	NA NA NA 23/5 28/4 37/3	Maintenance Phase SAE's: 1. 11% 2. 4% 3. 5% 4. 0% Gastrointestinal: 1. 0% 2. 2% 3. 2% 4. 7% Edema: 1. 2% 2. 6% 3. 14% 4. 2% Hypokalemia: (K<3.5 meq/L) 1. 0% 2. 10% 3. 11% 4. 0% 95% CI and p values NR for all outcomes		**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear due to OL phase. OL phase followed by maintenance phase in which subjects were randomized 4:4:4:7 in a double blind manner. Weekly kits containing 8 boxes with 3 sachets of SZC per box were assigned via an IVRS/IWRS. Baseline demographics similar between groups. Performance Bias: Low. Oral placebo powder had the exact same appearance, taste, odor, and mode of administration as SZC. The first dose was administered in the clinic so staff could train the subject how to reconstitute the product for oral administration. Subsequent doses were administered as an outpatient. Detection Bias: Low. Assessments completed by Independent Data Monitoring Committee. Potassium levels sent to a central laboratory for analysis and verification. Attrition Bias: Low. Attrition rates were similar in all study arms. Reasons for withdrawal due to adherence, adverse events, and hypo- or hyperkalemia were similar across all arms. Reporting Bias: Low. ITT analysis which included patients who discontinued study, but had at least 1 follow-up potassium level. Other Bias: Unclear. Sponsored by ZS Pharma, Inc. Two investigators who participated trial had financial interests or arrangements > $50,000 to disclose. **Applicability**: Patient: Included broad representation of patients in outpatient setting with hyperkalemia. Patients on dialysis, inpatients, or K >6.5 were excluded from this trial, so conclusions about safety or efficacy cannot be drawn in these populations. Intervention: OL dose of 10 gm TID was based on a dose finding from Study 1. Maintenance phase dosing (10 gm and 15 gm) was also based on data from Study 1. 5 gm dose included to establish a minimum effective dose.

								Comparator: Placebo. Direct comparison with patiromer or SPS would be helpful for comparative efficacy. Outcomes: Potassium levels reasonable to assess hyperkalemia. SZC doses only compared to placebo, not to each other. Setting: 44 sites in United States (80%), Australia (8%), and South Africa (12%)

Abbreviations [alphabetical order]: ARR = absolute risk reduction; CI = confidence interval; DB = Double-blind; DM = diabetes mellitus; GFR = estimated glomerular filtration rate; gm = gram; HF = Heart Failure; ITT = intention to treat; IVRS/IWRS = Interactive Voice/Web Response System; L = liter; MR = mean reduction compared to baseline; meq = milliequivalents; mITT = modified intention to treat; mmol = Millimole; MC = Multi-Center; MP = Multi-Phase; N = number of subjects; NA = not applicable; NR = Not Reported; NNH = number needed to harm; NNT = number needed to treat; OL = Open Label; PC = Placebo-controlled; PP = per protocol; RAAIs = Renin-Angiotensin-Aldosterone Inhibitors; RCT = Randomized Controlled Trial; SAE = Serious Adverse Events; SPS = sodium polystyrene sulfonate; SZC = sodium zirconium cyclosilicate; yo = years old

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Appendix 1: Current Preferred Drug List

Generic	Brand	Formulation	Route	PDL
patiromer calcium sorbitex	VELTASSA	POWD PACK	ORAL	
sodium polystyrene sulfon/sorb	KIONEX	ORAL SUSP	ORAL	N
sodium polystyrene sulfon/sorb	SPS	ORAL SUSP	ORAL	N
sodium polystyrene sulfon/sorb	SPS	ENEMA	RECTAL	N
sodium zirconium cyclosilicate	LOKELMA	POWD PACK	ORAL	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to February Week 4 2019, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations March 04, 2019

1. Hyperkalemia/	2658
2. Cation Exchange Resins/	890
3. Sodium polystyrene sulfonate.mp.	195
4. Patiromer.mp.	93
5. Sodium zirconium cyclosilicate.mp.	43
6. 2 or 3 or 4 or 5	1121
7. 1 and 6	152
8. limit 7 to (english language and humans and "all adult (19 plus years)" and (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or 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 review"))	15

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

LOKELMA™ (sodium zirconium cyclosilicate) for oral suspension
Initial U.S. Approval: [2018]

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

LOKELMA is a potassium binder indicated for the treatment of hyperkalemia in adults. (1)

Limitation of Use

LOKELMA should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action. (1)

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

- Recommended starting dose is 10 g administered three times a day for up to 48 hours. (2.1)
- For maintenance treatment, recommended dose is 10 g once daily. (2.1)
- Adjust dose at one-week intervals as needed (by 5 g daily) to obtain desired serum potassium target range. (2.1)

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

- For oral suspension: 5 g per packet (3)
- For oral suspension: 10 g per packet (3)

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

None. (4)

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

- Gastrointestinal Adverse Events in Patients with Motility Disorders. (5.1)
- Edema. (5.2)

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

Most common adverse reactions with LOKELMA: mild to moderate edema. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

In general, other oral medications should be administered at least 2 hours before or 2 hours after LOKELMA. (2.2, 7, 12.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 5/2018

Appendix 4: Key Inclusion Criteria

Population	Adults with hyperkalemia
Intervention	Sodium zirconium cyclosilicate, patiromer, sodium polystyrene sulfonate
Comparator	Placebo
Outcomes	Rate of potassium reduction, mean serum potassium level
Timing	48 hours, 12 days, and 28 days
Setting	Outpatient

Patiromer and Sodium Zirconium Cyclosilicate

Goals:

- Restrict use of patiromer and sodium zirconium cyclosilicate (SZC) to patients with persistent or recurrent hyperkalemia not requiring urgent treatment.
- Prevent use in the emergent setting or in scenarios not supported by the medical literature.
- ~~Encourage use to optimize medications with demonstrated evidence of mortality reduction in heart failure with reduced ejection fraction.~~

Length of Authorization:

- 6 to 12 months

Requires PA:

- Patiromer and Sodium Zirconium Cyclosilicate

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 continuation of therapy previously approved by the FFS program (patient already on patiromer or Sodium Zirconium Cyclosilicate (SZC))?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code. Go to #3	
3. Does the patient have persistent or recurrent serum potassium of ≥5.5 mEq/L despite a review for discontinuation of medications that may contribute to hyperkalemia (e.g., potassium supplements, potassium-sparing diuretics, nonsteroidal anti-inflammatory drugs)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
4. Has the patient tried and failed or cannot tolerate sodium polystyrene sulfonate (SPS)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Does the patient have hyperkalemia requiring emergency intervention (serum potassium ≥6.5 mEq/L)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #6
6. Is the request for patiromer?	**Yes:** Go to # 7	**No:** Go to # 8
~~6.~~7. Does the patient have hypomagnesemia (serum magnesium < 1.4 mg/dL)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #~~8~~7
~~7.~~8. Does the patient have a severe GI disorder (i.e., major GI surgery (e.g., large bowel resection), bowel obstruction/impaction, swallowing disorders, gastroparesis, or severe constipation)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve up to 6 months

Renewal Criteria		
1. Is the patient's potassium level < 5.1 mEq/L and has this decreased by at least 0.35 mEq/L from baseline?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T Review: *05/19~~7~~ (DM), 05/16 ~~(EL/MH)~~*
Implementation: *TBD, 8/16, 7/1/16*

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Salem, Oregon 97301-1079
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Drug Class Update: Non-statins for Management of Blood Cholesterol

Date of Review: May 2019

Date of Last Review: January 2018 (PCSK9 Inhibitors)
November 2016 (Non-statins)
End Date of Literature Search: March 1, 2019

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

Purpose for Class Update:
Since the last review, new data has been published evaluating non-statin agents as add on therapy to improve cardiovascular (CV) outcomes and reduce CV mortality. Additionally, recently published guidelines for hyperlipidemia management have new recommendations for the use of non-statin therapy. These data and any additional new comparative efficacy or harms data published since the last review will be evaluated.

Research Questions:
- Is there any new evidence for non-statin lipid-lowering agents in reducing cardiovascular (CV) outcomes or mortality in adult patients being treated for the primary or secondary prevention of CV disease?
- Is there any new comparative evidence for the efficacy or harms of non-statin lipid-lowering agents in patients being treated for the primary or secondary prevention of CV disease?
- Are there subpopulations of patients based on demographics (e.g., age, sex, race, and diagnoses) for which one non-statin agent is more effective or associated with more harm than other non-statin agents?

Conclusions:
PCSK9 Inhibitors
- 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).[1]
- 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) and x

Ezetimibe
- There is moderate quality evidence that ezetimibe has a modest benefit in reducing major adverse cardiovascular events (MACE) (relative risk [RR] 0.94; 95% CI 0.90 to 0.98; ARR 1.7%; NNT 59) compared to placebo. There is high-quality evidence of no difference in all-cause mortality (RR 0.98; 95% CI 0.91 to 1.05)

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and moderate quality evidence of no difference in CV mortality (RR 1.00; 95% CI 0.89 to 1.12). There was moderate quality evidence of a decrease risk of non-fatal myocardial infarction (MI; RR 0.88; 95% CI 0.81 to 0.95; ARR 1.3%; NNT 77) and non-fatal stroke (RR 0.83; 95% CI 0.71 to 0.97; ARR 0.5%; NNT 200).[2]

- There is insufficient evidence to make conclusions about the effectiveness of ezetimibe in those without atherosclerotic cardiovascular disease (ASCVD).

Niacin

- There is high quality evidence that niacin does not reduce overall mortality (RR 1.05; 95% CI 0.97 to 1.12) compared to placebo in people with or at risk of cardiovascular disease (CVD).[3] There is moderate quality evidence that niacin does not decrease the risk of fatal or non-fatal MI or CV mortality, high-quality evidence that niacin does not reduce non-cardiovascular mortality and low quality evidence that niacin does not reduce non-fatal or fatal stroke.
- There is moderate quality evidence of an increase in flushing, pruritus, rash, headache, gastrointestinal symptoms, new onset diabetes and discontinuations due to adverse events (absolute risk increase [ARI] 12%/number needed to harm [NNH] 9) with niacin compared to placebo.

Fibrates

- There is moderate quality evidence of a reduction in the primary composite CV outcome of CVD death, non-fatal with fibrates compared to placebo (RR 0.84; 95% CI 0.74 to 0.96; ARR 1%; NNT 100).[4] This difference is modest (<1%) in patients with a low baseline CV risk of 5% or lower and seems to apply to fibrates when used as monotherapy. There was no difference in CV events when including only trials that used fibrates in addition to statins (RR 1.01; 95% CI 0.78 to 1.31).
- There is low quality evidence of no difference in overall mortality (RR 1.01; 95% CI 0.81 to 1.26) and no effect on non-CVD mortality (RR 1.00; 95% CI 0.68 to 0.92) with fibrate therapy.[4]
- Low quality evidence suggests that fibrates are not associated with an increased risk for discontinuations due to adverse effects (RR 1.38; 95% CI 0.71 to 2.68).

Omega-3 Fatty Acids

- High quality evidence demonstrates no reduction in mortality with long chain omega-3 (LCn3) supplementation (RR 0.98, 95% CI 0.90 to 1.03).[5]
- There are three new randomized controlled trials (RCTs) evaluating the effects of omega-3 fatty acid supplementation on CV outcomes in both primary and secondary prevention with inconsistent findings.
- There is moderate quality evidence that omega-3 fatty acids do not decrease a composite CV outcome compared to placebo in adults with or without diabetes and without any evidence of ASCVD (HR 0.92; 95% CI 0.80 to 1.06).[6,7]Mean follow-up was almost eight years in adults with diabetes and 5.3 years in adults without diabetes
- 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.[8] 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 is needed to confirm these findings.

Recommendations:

- Update prior authorization criteria to be consistent with the new evidence for use of non-statins to prevent ASCVD events (**Appendix 6**)
- Consider retiring the prior authorization criteria for lomitapide and mipomersen due to no utilization
- Make gemfibrozil non-preferred due to safety concerns with use in combination with statin therapy
- Review comparative costs in executive session

Summary of Prior Reviews and Current Policy:

- Current PA polices for PCKS9 inhibitors, lomitapide and mipomersen, and omega-3 fatty acids are included in Appendix 6.
- 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). Due to the modest improvement seen and cost evaluation, ezetimibe remains non-preferred.
- 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.
- Moderate quality evidence shows PCSK9 inhibitors are efficacious at reducing LDL-C by over 50% from baseline in high risk patients.
- There is moderate quality evidence from one large, good quality trial with a median duration of follow-up of 26 months that evolocumab added on to statin therapy reduces non-fatal CV events compared to placebo with a modest magnitude of benefit (ARR 1.5%; NNT 67) in patients with clinically evidence CVD at high risk for recurrence.
- Evolocumab and alirocumab currently require prior authorization for approval to limit use to patients with CVD or familial hypercholesterolemia at high risk for CV events who require additional LDL-C lowering despite use of other lipid-lowering agents, including statins.

Background

Hypercholesterolemia, and especially elevated low-density lipoprotein cholesterol (LDL-C), is associated with increased risk of ASCVD. Prevention of ASCVD events involves optimization of treatments that have proven benefits on reduction in ASCVD events and/or cardiovascular (CV) mortality. Until 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 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.

Currently, only ezetimibe 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 (**Table 1**). 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.[11] 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.

Evolocumab (Repatha®) and alirocumab (Praluent®) are subcutaneously injected human monoclonal antibodies that reduce LDL-C by inhibiting PCSK9.[12,13] PCSK9 promotes the degradation of the LDL receptor, resulting in an increase in plasma LDL-C. Both agents are effective at lowering LDL-C with reductions of up to 60% when combined with statin therapy. Both agents are approved as an adjunct with other lipid-lowering therapies (statins, ezetimibe) for primary hyperlipidemia (heterozygous familial hypercholesterolemia) and clinical ASCVD who require additional lowering of LDL-C. In 2017, evolocumab was also 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 trial.[12,14] The ODYSSEY OUTCOMES trial, published since the last review, evaluated the effects on CV outcomes of alirocumab given in combination with statin therapy.[15]

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 - 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.[16] 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®) and icosapent ethyl are two FDA-approved legend drugs for the treatment of severe hypertriglyceridemia. Icosapent ethyl is a form of eicosapentaenoic acid (EPA) while other products have both EPA and docosahexaenoic acid (DHA). There have been several new RCTs evaluating omega-3 fatty acids on CV outcomes in both primary and secondary prevention.

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted from January 1st, 2016 through March 1st, 2019. 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, BMJ Clinical Evidence, 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, evidence-based guidelines, and randomized controlled trials (RCTs) evaluating clinical cardiovascular (CV) outcomes. Randomized controlled trials of surrogate outcomes will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
After review, **21** 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), outcome studied (e.g., non-clinical), or included in a systematic review from a trusted source (DERP).

PSCK9 Inhibitors:

1. A systematic review and update was conducted by the Drug Effectiveness Review Project (DERP) evaluating RCTs and systematic reviews focusing on adults with familial or nonfamilial hypercholesterolemia who have not achieved recommended LDL-C serum levels despite lipid-lowering therapy.[1] Placebo controlled trials were included if the primary outcome was CV disease. Overall, there is consistent evidence that PCSK9 inhibitors are more effective than ezetimibe, standard of care and placebo at reducing LDL-C levels in various populations with both familial and nonfamilial hypercholesterolemia. In patients with heterozygous familial hypercholesterolemia (HeFH) or homozygous familial hypercholesterolemia (HoFH), there was insufficient evidence evaluating alirocumab for all outcomes. There was low quality evidence that evolocumab significantly reduced LCL-C compared to standard of care after 48 weeks of treatment (mean difference -55.7%) in patients with HeFH with insufficient evidence on CV outcomes or in HoFH. In statin-intolerant patients, there is low evidence that evolocumab resulted in no difference in CV events compared to ezetimibe based on three RCTs. The authors concluded high quality evidence based on the ODYSSEY OUTCOMES trial of a decrease in CV events with alirocumab versus placebo in patients with nonfamilial hypercholesterolemia (9.5% vs. 11.1%; HR 0.85; 95% CI 0.78 to 0.93) and moderate quality evidence of similar risks of death from CV causes (2.5% vs. 2.9%). Mortality was statistically significantly lower in the alirocumab group compared to placebo (3.5% vs. 4.1%; HR 0.85; 95% CI 0.73 to 0.99) with a similar measure of association (HR 0.85 vs. HR 0.88). Prespecified subgroup analyses concluded no difference in the primary CV composite outcome between those who were younger than 65 years and older than 65, men and women, and different ethnicities. Additionally, based on the FOURIER trial, there is high quality evidence of a statistically significant 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). The absolute risk reduction is small in both trials. In regard to differences in subgroups, there is high quality evidence of similar reductions in CV events with evolocumab versus placebo in patients with and without diabetes and similar LDL-C reductions with alirocumab versus ezetimibe in men and women. There remains insufficient head to head comparative data on the effectiveness and harms of the PCSK9 inhibitors.

   The DERP review also identified a Cochrane systematic review that included 16 relevant trials on alirocumab and evolocumab. The analyses suggested a class effect of PCSK9 inhibitors. Although populations were combined (familial and nonfamilial) two additional agents were included (bococizumab and RG7652), the results showed similar magnitude of effect and direction. PCSK9 inhibitors demonstrated a significant reduction in LDL-C compared to ezetimibe (mean % change of -30.20%; 95% CI -34.18 to -26.23) and compared to ezetimibe plus statins (mean % difference of -39.20%; 95% CI -56.15 to -22.26). Additionally, there was a reduction in CV events with PCSK9 inhibitors compared to ezetimibe plus statins (OR 0.45; 95% CI 0.27 to 0.75) and an increased risk of adverse events (OR 1.18; 95% CI 1.05 to 1.34).

   There was very low evidence making it difficult to form any conclusions about treatment effects on CV outcomes in the following populations: alirocumab in statin-intolerant patients, alirocumab and evolocumab versus ezetimibe inpatients with nonfamilial hypercholesteremia, alirocumab versus other lipid-lowering regimens, and evolocumab versus ezetimibe in nonfamilial hypercholesterolemia.

2. Another high-quality systematic review evaluated the effects of PCSK9 inhibitors on major adverse cardiovascular events (MACE).[17] Forty-six RCTs were included in the meta-analysis. Pre-defined subgroup analysis was done to examine the effect based on drug type, follow-up duration, and prevention type (primary versus secondary). Twenty-two trials included alirocumab and 19 included evolocumab. The remaining trials evaluated either bococizumab, which has been discontinued from development, or drugs not yet approved. Overall, PCSK9 inhibitors were associated with a significantly reduced risk of MACE (RR 0.84; 95% CI 0.79 to 0.89; ARR 4.7% over 10 years). The quality of the evidence was rated as moderate and downgraded due to indirectness of populations which varied across trials. None of the subgroup analysis showed significant heterogeneity based on drug type, study design, population, or type of control. Therefore, the authors concluded that the effect of PCSK9 inhibitors appears to be a class effect. There was also

low-quality evidence that PCSK9 inhibitors significantly reduced non-fatal MI (RR 0.83; 95% CI 0.74 to 0.93; ARR 3.5%) and any stroke (RR 0.75; 95% CI 0.65 to 0.85; ARR 1.6%) over a 10-year time period.

Ezetimibe:

1. A Cochrane systematic review evaluated the efficacy and safety of ezetimibe for the prevention of CVD and all-cause mortality in patients with and without established CVD.[2] Overall, 26 RCTs (n=23,499) were included in the review. Three of the studies were multi-center, two were conducted in the United States (US), and the remainder were performed outside of the US. Most studies had a follow up of one to two years. The largest study was IMPROVE-IT, which included a median follow-up of six years. Fourteen studies included patients with existing ASCVD. None of the studies included ezetimibe as monotherapy. All of the trials compared ezetimibe plus other lipid-modifying drugs (majority of them were statins; n=25) to lipid-modifying drugs alone or in combination with placebo. The majority of studies had low or unclear risk of bias. Eight studies were open-label design and had a high risk of performance bias.

   Overall, there was moderate quality evidence from 10 studies that ezetimibe had a lower risk of major adverse cardiovascular events (MACE) (RR 0.94; 95% CI 0.90 to 0.98; ARR 1.7%; NNT 59). [2] Results were largely driven by the IMPROVE-IT trial, which included differences in non-fatal MI, non-fatal stroke and urgent coronary revascularizations. There was high-quality evidence of no difference in all-cause mortality (RR 0.98; 95% CI 0.91 to 1.05) and moderate quality evidence of no difference in CV mortality (RR 1.00; 95% CI 0.89 to 1.12). [2] There was moderate quality evidence of a decrease risk of non-fatal MI (RR 0.88; 95% CI 0.81 to 0.95; ARR 1.3%; NNT 77) and non-fatal stroke (RR 0.83; 95% CI 0.71 to 0.97; ARR 0.5%; NNT 200).[2] A subgroup analysis showed no difference in primary outcomes between those with and without established ASCVD. However, fewer individuals were included without ASCVD and confidence intervals were wide. Therefore, it remains difficult to make conclusions about the effectiveness of ezetimibe in those without ASCVD.

   Pooling of adverse events was not possible due to heterogeneity in the definition of adverse events. However, the individual studies showed no difference in adverse events. There was no significant difference found in the following events: liver injury, myopathy, rhabdomyolysis, cancer, and discontinuation due to adverse events. However, the quality of evidence for liver injury and myopathy is low and very low due to imprecision and risk of bias. Results of sensitivity analyses using only studies at low risk of bias, random-effects modeling, and excluding studies with missing data did not change estimates for most outcomes. [2]

Niacin:

1. A Cochrane review assessed the effectiveness of niacin therapy versus placebo or other lipid modifying drugs, administered as monotherapy or add-on to statin based therapy in adults with or at risk of CVD.[3] Twenty-three RCTS (n=39,195) were included in the meta-analysis. The majority of trials included a mixed population, evaluating niacin in both primary and secondary prevention of CVD. The duration of treatment ranged from 6 months to 6 years, and 19 trials applied one or more methods to reduce skin flushing due to niacin. Fourteen of the trials were placebo-controlled, and the remaining 9 compared standard treatment without a placebo to niacin. The majority of studies had low or unclear risk of bias and eleven trials had a high risk of attrition bias. The majority of trials also had high risk of bias due to missing data.

There was high quality evidence from 12 studies that niacin did not reduce overall mortality (RR 1.05; 95% CI 0.97 to 1.12). [3] Sensitivity analyses did not change the primary outcome results, and meta-regression analysis did not show a significant effect modification by duration, proportion of patients with established CVD, or proportion of patients on background statin therapy. The results were robust to sensitivity analyses using different assumptions for missing data. Additionally, there was moderate quality evidence that niacin did not decrease the risk of fatal or non-fatal MI or CV mortality, high-quality evidence that niacin did not reduce non-cardiovascular mortality, and low quality of evidence that niacin did not reduce non-fatal or fatal stroke. Additionally, there was moderate quality evidence of an increase in flushing, pruritus, rash, headache, gastrointestinal symptoms, new onset diabetes and discontinuations due to adverse events (ARI 12%/ NNH 9). [3]

Fibrates:

1. A 2016 Cochrane review and meta-analysis aimed to evaluate the clinical benefits and harms of fibrate monotherapy versus placebo or usual care or fibrates in combination with other lipid-modifying drugs versus other lipid-modifying drugs alone for the primary prevention of CVD morbidity and mortality.[4] Included primary prevention RCTs were required to have fewer than 10% of participants with established CVD. The primary outcome was a composite CV outcome including CVD death, non-fatal MI or non-fatal stroke. Six eligible trials were identified including 16,135 individuals. The mean treatment duration and follow-up of participants across trials was 4.8 years. Three trials included fenofibrate and one included gemfibrozil. The other two trials included drugs not available in the U.S. The majority of trials had low risk of bias. Two trials had high attrition bias and two had a high risk of other bias due to conflicts of interest.

   There was moderate quality evidence of a reduction in the primary composite CV outcome with fibrates compared to placebo (RR 0.84; 95% CI 0.74 to 0.96; ARR 1%; NNT 100). [4] This difference is modest (<1%) in patients with a low baseline risk of 5% or lower and seems to apply to fibrates when used as monotherapy. There was low quality evidence of no difference in overall mortality (RR 1.01; 95% CI 0.81 to 1.26) and no effect on non-CVD mortality (RR 1.00; 95% CI 0.76 to 1.33). [4] Sensitivity analyses focusing only on trials that reported concealed treatment allocation showed no difference CV events (RR 1.00; 95% CI 0.77 to 1.30). [4] There was also no difference in CV events when including only trials that used fibrates in addition to statins (RR 1.01; 95% CI 0.78 to 1.31). Very low-quality evidence suggests that fibrates are not associated with an increased risk for discontinuations due to adverse effects (RR 1.38; 95% CI 0.71 to 2.68). [4]

Omega-3 fatty acids:

1. A Cochrane systematic review assessed effects of increased intake of fish- and plant-based omega-3 fatty acids on all-cause mortality, CV events, and lipids.[5] Seventy-nine RCTs (n=112,059) that lasted at least 12 months and compared supplementation and/or advice to increase omega-3 intake versus usual or lower intake were included. Trials were of 12 to 72 months' duration and included adults at varying cardiovascular risk, mainly in high-income countries. Most studies assessed long chain omega-3 (LCn3) supplementation (n=62), but some used LCn3- or alpha-linolenic acid (ALA)-rich or enriched foods or dietary advice compared to placebo or usual diet. Additionally, LCn3 was supplemented through capsules or medicinal oils. Doses of LCn3 ranged from 0.5 grams per day to greater than 5 grams per day. Twenty-five trials were deemed to be at low risk of bias. The remainder were moderate to high risk of bias.

   High quality evidence showed little or no effect on all-cause mortality (RR 0.98, 95% CI 0.90 to 1.03). Sensitivity analyses using fixed effect meta-analysis, removing studies not at low risk of bias did not change the lack of effect on all-cause mortality. The lack of effect did not differ by primary or

secondary prevention or mode of intervention (dietary advice versus supplementation). Moderate quality evidence suggests no significant effect on cardiovascular mortality (RR 0.95, 95% CI 0.87 to 1.03) and high-quality evidence shows no significant effect on cardiovascular events (RR 0.99, 95% CI 0.94 to 1.04).[5]

The funnel plots for all three of these outcomes suggest that some smaller studies with more participants experiencing the outcome in the intervention group were missing. If these studies were included, it could possibly increase the relative risk closer to null. Additionally, moderate quality evidence suggests no significant effect on CHD mortality, CHD events, stroke, or arrhythmias. There was no suggestion of a dose response or important effects from subgroup analysis or meta-regression. Studies also demonstrated that increasing ALA intake probably makes little or no difference in all-cause mortality or CV mortality. However, increased ALA probably does not reduce risk of cardiovascular events (from 4.8% to 4.7%, RR 0.95, 95% CI 0.83 to 1.07, low-quality evidence with greater effects in trials at low summary risk of bias), and probably reduces risk of arrhythmia (3.3% to 2.6%, RR 0.79, 95% CI 0.57 to 1.10). [5] Authors also determined that there was no evidence that increasing LCn3 or ALA altered serious adverse events, adiposity or lipids, except LCn3 reduced triglycerides by approximately 15% in a dose-dependent way (high-quality evidence). [5]

2. The Omega-3 Treatment Trialists' Collaboration was a meta-analysis based on aggregated study-level data from all large RCTS of omega-3 fatty acids for the prevention of CVD.[18] A total of ten trials were included in the analysis (n=77,917). Two trials did not use a placebo-treated control group. The remaining were given a low risk of bias. One trial evaluated EPA alone while the others included a combination of EPA and DHA. Overall, there was no significant effect seen in any CHD event (RR 0.96; 95% CI 0.90 to 1.01) or any individual CHD events (CHD death, nonfatal MI, stroke or revascularization) with omega-3 fatty acids compared to placebo or control. No significant effect was observed in any of the prespecified subgroups.

Guidelines:

ACC/AHA Guidelines on the Management of Blood Cholesterol (Grundy 2018)

Updated recommendations for reducing ASCVD risk were released following from the American College of Cardiology (ACC) / American Heart Association (AHA) in 2018.[9] Guidelines were updated based on a systematic review that identified 10 new RCTs in patients with clinical ASCVD or at high risk of ASCVD.[19] The pre-specified primary outcome was a composite of fatal CV events, nonfatal MI, or nonfatal stroke. RCTs were assessed for bias using the Cochrane Collaboration Risk of Bias Tool. A meta-analysis was not done, and direct comparisons of the included RCTs could not be performed. Results from the systematic review will be incorporated into guideline recommendations below.

Statin Therapy:

Statins remain the cornerstone of therapy and should be optimized in all patients with ASCVD and at high risk for ASCVD. Statins are recommended in the four patient management groups, which were modified slightly from the previous guidelines to allow for more personalized care and include more detailed risk assessments (**Table 1**).

Table 1: Statin Benefit Groups

Statin Benefit Group	Recommended Treatment
Clinical ASCVD	High-intensity statin (≤ 75 y/o); moderate- to high-intensity statin if > 75 y/o
Severe Hypercholesterolemia (LDL-C ≥ 190 mg/dl)	Maximally tolerated statin

Diabetes age 40-75 and LDL-C ≥ 70 mg/dl	Moderate-to high-intensity statin (based on ASCVD risk factors)
Primary Prevention (Adults 40-75 years with LDL-C ≥70)	Moderate- to high-intensity statin based on risk discussion, 10-year ASCVD risk, and ASCVD risk enhancers
Abbreviations: ASCVD: atherosclerotic cardiovascular disease; LDL-C: low density lipoprotein cholesterol; y/o: years old	

Non-statin Therapy:

A significant change in the guidelines is the addition of an LDL-C threshold of 70 mg/dl to consider adding a non-statin in clinical ASCVD. This recommendation comes from the general idea that "lower is better" for LDL-C, particularly in high-risk patients. Very high-risk ASCVD is a new category and includes a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions (**Table 2**).[9] The guideline recommendation is to add ezetimibe to maximally tolerated statin therapy as a first step in lowering LDL-C, followed by a PCSK9 inhibitor if LDL-C remains ≥ 70 mg/dl on both statin and ezetimibe therapy for very high risk patients only.[9]

Table 2: Very High-Risk ASCVD

Major ASCVD events	**High-Risk Conditions**	
Recent ACS	Age ≥65	Diabetes mellitus
History of MI	HoFH	Hypertension
History of ischemic stroke	History of prior CABG or PCI	CKD Heart failure
Symptomatic PAD	Current Smoking	Persistently elevated LDL-C despite statin + ezetimibe

Abbreviations: ACS: acute coronary syndrome; ASCVD: atherosclerotic cardiovascular disease; CABG: coronary artery bypass graft; CKD: chronic kidney disease; HoFH: homozygous familial hypercholesterolemia LDL-C: low density lipoprotein cholesterol; MI: myocardial infarction; PAD: peripheral artery disease; PCI: percutaneous coronary intervention

Ezetimibe and the PCSK9 inhibitors are recommended as add on therapy as there is new evidence for reduced morbidity. Based on the IMPROVE-IT trial (**Tables 3 and 4**), the evidence review committee concluded that ezetimibe modestly reduced ASCVD risk over 7 years (ARR 2%) when applied to a post-ACS population treated with background statins. Additionally, post hoc analysis suggested that adults with the greatest burden of risk factors experienced the largest reduction in ASCVD risk with ezetimibe. High risk individuals experienced an ARR of 6.3% over 6 years. [19]

Table 3: Characteristics of Cardiovascular Outcome trials for Non-statins[11,14,15]

	FOURIER	**ODYSSEY**	**IMPROVE-IT**
Non-Statin Study Drug	evolocumab	alirocumab	ezetimibe
Patient Population	MI, stroke or PAD	4-52 weeks post-ACS	ACS (prior 10 days)
Median LDL-C	92 mg/dl	92 mg/dl	95 mg/dl
% on High Intensity Statin	69%	89%	6%
% on Ezetimibe	5%	3%	-
Study Duration	26 months	34 months	6 years

Abbreviations: ACS: acute coronary syndrome: LDL-C: low density lipoprotein cholesterol MI: myocardial infarction; PAD: peripheral artery disease

Four new trials evaluated the effectiveness of PCSK9 inhibitors. [19] However, two of these trials evaluated bococizumab which was discontinued in the development stage due to the formation of antidrug antibodies resulting in an attenuation of LDL-C lowering over time. The FOURIER trial demonstrated a significant LDL-C reduction (median 59%) and reduction in composite CV outcome (ARR 1.5%; NNT 67) with evolocumab plus maximally tolerated statin therapy compared to statin monotherapy in patients with clinically evident CVD. [19] There was no difference in all-cause death or death due to CVD. The ODYSSEY OUTCOMES trial evaluated alirocumab in patients with recent ACS and an LDL-C of ≥ 70 mg/dl on maximally tolerated statin. Similar to the FOURIER trial, LDL-C was significantly reduced from baseline, and there was a decrease in the composite CV outcome (ARR 1.6%; NNT 63) with a median follow-up period of 2.8 years. There was also a small decrease in all-cause mortality (3.5% vs. 4.1%; HR 0.85; 95% CI 0.73 to 0.98; ARR 0.6%; NNT 167). [19] Differences in mortality compared to evolocumab could be due to the different patient populations (recent ACS vs. chronic stable CVD). In both PCSK9 outcome trials, rates of serious adverse events, neurocognitive side effects, new onset diabetes, and discontinuations due to adverse events were not different between drug and placebo. Injection site reactions were more common than both PCSK9 inhibitors compared to placebo.

Table 4: Summary of Results from Cardiovascular Outcome Trials[11,14,15]

Outcome	Evolocumab ARR/NNT	Alirocumab ARR/NNT	Ezetimibe ARR/NNT
CV Composite Outcome	1.5% / 67	1.6% / 63	2% / 50
CV Death	NS	NS	NS
Death from any cause	NS	0.6% / 167	NS
Myocardial infarction	1.2% /84	1% / 100	1.7% / 59
Stroke	0.4% / 250	0.4% / 250	NS

The following recommendations are included in the guidelines as a result of this new data (descriptions of how recommendations and quality of evidence were graded are in Appendix 5 : [9]

Ezetimibe:

- In very-high risk ASCVD, it is reasonable to add ezetimibe to maximally tolerated statin therapy when the LDL-C remains ≥ 70 mg/dl (Class of Recommendation [COR] IIa; Level of Evidence [LOE] B-R).
- In patients with clinical ASCVD (not at very-high risk) who are receiving maximally tolerated statin therapy and whose LDL-C remains ≥ 70 mg/dl, it is reasonable to add ezetimibe (COR IIb; LOE B-R).
- In patients with severe primary hypercholesterolemia (baseline LDL ≥ 190 mg/dl), who achieve less than a 50% reduction in LDL-C and/or have an LDL-C remaining ≥ 100 mg/dl on maximally tolerated statin, it is reasonable to add ezetimibe (COR IIa; LOE B-R).
- In adults with diabetes mellitus and 10-year ASCVD risk of 20% or higher, it may be reasonable to add ezetimibe to maximally tolerated statin therapy (COR IIb; LOE C-LD).

PCSK9 Inhibitors

- In patients at very high risk whose LDL-C level remains ≥70 mg/dl on maximally tolerated statin and ezetimibe therapy, adding a PCSK9 inhibitor is reasonable, although the long-term safety (>3 years) is uncertain and cost effectiveness is low at mid-2018 list prices (COR IIa; LOE A).

- In patients with severe primary hypercholesterolemia and a baseline LDL-C of 220 mg/dl or higher and who achieve an on-treatment LDL-C of 130 mg/dl or higher while receiving maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered (COR IIb; LOE C-LD).
- In patients 30 to 75 years of age with HeFH and with an LDL-C level of 100 mg/dL or higher while taking maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered (COR IIb; LOE B-R).

Although no RCT specifically tested the strategy of ezetimibe first and then a PCSK9 inhibitor, ezetimibe was allowed at entry along with statin therapy in both PCSK9 inhibitor trials but occurred in very small numbers (3% and 5% respectively). The strategy of ezetimibe before PCSK9 inhibitor is recommended because ezetimibe is widely available as a generic drug and has proven safety and tolerability.

The ACC/AHA Systematic review identified two large RCTs that evaluated niacin in addition to statin and/or ezetimibe in the past several years.[19] The AIM-HIGH trial was conducted in patients with clinical ASCVD and was stopped early due to a lack of efficacy. The HPS2-THRIVE study also assessed niacin as add on therapy to statin and/or ezetimibe in patients with established ASCVD. Similar to AIM-HIGH, participants on niacin saw no reduction in CVD events. The combination of niacin and laropiprant (a prostaglandin antagonist used to reduce flushing) was associated with an increased risk of serious adverse effects, including worsening diabetic control, gastrointestinal, muscle and skin abnormalities, as well as increased risk of infection and bleeding. The guidelines do not include niacin as a recommended add-on therapy.

New FDA Safety Alerts:
None identified

New formulations or Indications:
In December, 2017 FDA approved evolocumab to reduce the risk of MI, stroke and coronary revascularization in adults with established CVD based on the results of the FOURIER trial.[12]

In April 2019, a new chewable bar formulation of colesevelam (Welchol) was FDA approved.[20] Each bar (chocolate, strawberry or caramel flavors) contains approximately 80 calories per bar and should be taken with a meal. It is approved as adjunct to diet and exercise to reduce LDL-C in adults with primary hyperlipidemia and to improve glycemic control in patients with type 2 diabetes mellitus. The approval was based on studies conducted with colesevelam tablets. The effect on colesevelam on cardiovascular morbidity or mortality has not been demonstrated.

Randomized Controlled Trials:
A total of 339 citations were manually reviewed from the initial literature search. After further review, 335 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 4 trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 5. Summary of Clinical Trials Evaluating Clinical CV Outcomes

Study	Comparison	Population	Primary Outcome	Results	
REDUCE-IT[8] DB, PC, MC, RCT	Icosapent ethyl 2gm BID vs. placebo Median duration: 4.9 years	Adults ≥ 45 y/o with CVD or ≥ 50 y/o with DM and at least one additional risk factor, on background statin therapy with TG 150-499 mg/dl and LDL 41-100 mg/dl (n=8,179)	Composite of CV death and nonfatal MI or stroke, coronary revascularization or unstable angina	<u>Composite CV Outcome:</u> Icosapent: 705 (17.2%) Placebo: 901 (22%) HR 0.75; 95% CI 0.68 to 0.83 ARR 4.8% / NNT 21 <u>Death from any cause:</u> Icosapent: 274 (6.7%) Placebo: 310 (7.6%) HR 0.87; 95% CI 0.74 to 1.02	<u>CV death:</u> Icosapent: 174 (4.3%) Placebo: 213 (5.2%) HR 0.80; 95% CI 0.66 to 0.98 ARR 0.9% / NNT 112 <u>Atrial fibrillation:</u> Icosapent: 215 (5.3%) Placebo: 159 (3.9%) ARI 1.4% / NNH 72 <u>Peripheral edema:</u> Icosapent: 267 (6.5%) Placebo: 203 (5.0%) ARI 1.5% / NNH 67
ASCEND[6] RCT	Omega-3 fatty acids 1gm daily versus placebo Mean follow up of 7.4 years	Adults ≥ 40 y/o with diabetes but no evidence of ASCVD (n=15,480)	First serious vascular event (nonfatal MI or stroke, TIA or vascular death)	<u>Serious vascular event:</u> Omega-3: 689 (8.9%) Placebo: 712 (9.2%) RR 0.97; 95% CI 0.87 to 1.08 There were no significant differences in serious adverse events	
ODYSSEY OUTCOMES[15] RCT, DB, PC, MC	Alirocumab 75 mg or 150 mg SQ Q2W vs. placebo Median duration: 2.8 years	Adults with LDL ≥ 70 mg/dl, non-HDL ≥ 100 mg/dl or apolipoprotein B ≥ 80 mg/dl, hospitalized 1-12 months prior for ACS on maximally tolerated statin (n=18,924)	Composite of CHD death, non-fatal MI, fatal and non-fatal ischemic stroke, and unstable angina requiring hospitalization	<u>CV composite outcome:</u> Alirocumab: 903 (9.5%) Placebo: 1052 (11.1%) HR 0.85; 95% CI 0.78 to 0.93 ARR 1.6% / NNT 63	<u>Death from CV causes:</u> Alirocumab: 240 (2.5%) Placebo: 271 (2.9%) HR 0.88; 95% CI 0.74 to 1.05 <u>Death from any cause:</u> Alirocumab: 334 (3.5%) Placebo: 392 (4.1%) HR 0.85; 95% CI 0.73 to 0.98 ARR 0.6% / NNT 167
VITAL[7] RCT, PC, DB	Omega-3 fatty acids (1 gm per day) vs. placebo Median duration: 5.3 years	Men ≥ 50 y/o and women ≥ 55 y/o (primary prevention) (n=25,871)	Composite of MI, stroke and death from CV cause	<u>CV composite outcome:</u> Omega-3 fatty acids: 386 (3.0%) Placebo: 419 (3.2%) HR 0.92; 95% CI 0.80 to 1.06	

Abbreviations: ACS = acute coronary syndrome; ARI = absolute risk increase; ARR = absolute risk reduction; ASCVD = atherosclerotic cardiovascular disease; CHD = coronary heart disease; CI = confidence interval; CV = cardiovascular; CVD = cardiovascular disease; DB = double blind; DM = diabetes mellitus; HDL = high density lipoprotein cholesterol; HR = hazard ratio; LDL-C = low density lipoprotein cholesterol; MC = multi-centered; mg = milligram; MI = myocardial infarction; NNH = number needed to harm; NNT = number needed to treat; PC = placebo controlled; Q2W = every 2 weeks; QMO = every month; RCT = randomized controlled trial; RR = relative risk; SQ = subcutaneously; TIA = transient ischemic attack; TG = triglycerides; y/o = years old

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Appendix 1: Current Preferred Drug List

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

fenofibrate,micronized	FENOFIBRATE	CAPSULE	N
fenofibric acid	FENOFIBRIC ACID	TABLET	N
fenofibric acid	FIBRICOR	TABLET	N
fenofibric acid (choline)	FENOFIBRIC ACID	CAPSULE DR	N
fenofibric acid (choline)	TRILIPIX	CAPSULE DR	N
icosapent ethyl	VASCEPA	CAPSULE	N
inositol	INOSITOL	TABLET	N
lomitapide mesylate	JUXTAPID	CAPSULE	N
niacin	NIACIN	CAPSULE ER	N
niacin	NIACIN ER	TAB ER 24H	N
niacin	NIASPAN	TAB ER 24H	N
niacin	NIACIN	TABLET	N
niacin	NIACOR	TABLET	N
niacin	NIACIN	TABLET ER	N
niacin	SLO-NIACIN	TABLET ER	N
omega-3 acid ethyl esters	LOVAZA	CAPSULE	N
omega-3 acid ethyl esters	OMEGA-3 ACID ETHYL ESTERS	CAPSULE	N

Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, Doyle RT Jr, Juliano RA, Jiao L, Granowitz C, Tardif JC, Ballantyne CM; REDUCE-IT Investigators. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. N Engl J Med. 2019 Jan 3;380(1):11-22. doi: 10.1056/NEJMoa1812792. Epub 2018 Nov 10.

Abstract
BACKGROUND:
Patients with elevated triglyceride levels are at increased risk for ischemic events. Icosapent ethyl, a highly purified eicosapentaenoic acid ethyl ester, lowers triglyceride levels, but data are needed to determine its effects on ischemic events.

METHODS:
We performed a multicenter, randomized, double-blind, placebo-controlled trial involving patients with established cardiovascular disease or with diabetes and other risk factors, who had been receiving statin therapy and who had a fasting triglyceride level of 135 to 499 mg per deciliter (1.52 to 5.63 mmol per liter) and a low-density lipoprotein cholesterol level of 41 to 100 mg per deciliter (1.06 to 2.59 mmol per liter). The patients were randomly assigned to receive 2 g of icosapent ethyl twice daily (total daily dose, 4 g) or placebo. The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina. The key secondary end point was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

RESULTS:
A total of 8179 patients were enrolled (70.7% for secondary prevention of cardiovascular events) and were followed for a median of 4.9 years. A primary end-point event occurred in 17.2% of the patients in the icosapent ethyl group, as compared with 22.0% of the patients in the placebo group (hazard ratio, 0.75; 95% confidence interval [CI], 0.68 to 0.83; P<0.001); the corresponding rates of the key secondary end point were 11.2% and 14.8% (hazard ratio, 0.74; 95% CI, 0.65 to 0.83; P<0.001). The rates of additional ischemic end points, as assessed according to a prespecified hierarchical schema, were significantly lower in the icosapent ethyl group than in the placebo group, including the rate of cardiovascular death (4.3% vs. 5.2%; hazard ratio, 0.80; 95% CI, 0.66 to 0.98; P=0.03). A larger percentage of patients in the icosapent ethyl group than in the placebo group were hospitalized for atrial fibrillation or flutter (3.1% vs. 2.1%, P=0.004). Serious bleeding events occurred in 2.7% of the patients in the icosapent ethyl group and in 2.1% in the placebo group (P=0.06).

CONCLUSIONS:
Among patients with elevated triglyceride levels despite the use of statins, the risk of ischemic events, including cardiovascular death, was significantly lower among those who received 2 g of icosapent ethyl twice daily than among those who received placebo. (Funded by Amarin Pharma; REDUCE-IT ClinicalTrials.gov number, NCT01492361).

Bowman L, Mafham M, Wallendszus K, Stevens W, Buck G, Barton J, Murphy K, Aung T, Haynes R, Cox J, Murawska A, Young A, Lay M, Chen F, Sammons E, Waters E, Adler A, Bodansky J, Farmer A, McPherson R, Neil A, Simpson D, Peto R, Baigent C, Collins R, Parish S, Armitage J. Collaborators ASCEND Study Collaborative Group, Effects of n-3 Fatty Acid Supplements in Diabetes Mellitus. N Engl J Med. 2018 Oct 18;379(16):1540-1550. doi: 10.1056/NEJMoa1804989. Epub 2018 Aug 26.

Abstract
BACKGROUND:
Increased intake of n-3 fatty acids has been associated with a reduced risk of cardiovascular disease in observational studies, but this finding has not been confirmed in randomized trials. It remains unclear whether n-3 (also called omega-3) fatty acid supplementation has cardiovascular benefit in patients with diabetes mellitus.

METHODS:
We randomly assigned 15,480 patients with diabetes but without evidence of atherosclerotic cardiovascular disease to receive 1-g capsules containing either n-3 fatty acids (fatty acid group) or matching placebo (olive oil) daily. The primary outcome was a first serious vascular event (i.e., nonfatal myocardial infarction or stroke, transient ischemic attack, or vascular death, excluding confirmed intracranial hemorrhage). The secondary outcome was a first serious vascular event or any arterial revascularization.

RESULTS:
During a mean follow-up of 7.4 years (adherence rate, 76%), a serious vascular event occurred in 689 patients (8.9%) in the fatty acid group and in 712 (9.2%) in the placebo group (rate ratio, 0.97; 95% confidence interval [CI], 0.87 to 1.08; P=0.55). The composite outcome of a serious vascular event or revascularization occurred in 882 patients (11.4%) and 887 patients (11.5%), respectively (rate ratio, 1.00; 95% CI, 0.91 to 1.09). Death from any cause occurred in 752 patients (9.7%) in the fatty acid group and in 788 (10.2%) in the placebo group (rate ratio, 0.95; 95% CI, 0.86 to 1.05). There were no significant between-group differences in the rates of nonfatal serious adverse events.

CONCLUSIONS:
Among patients with diabetes without evidence of cardiovascular disease, there was no significant difference in the risk of serious vascular events between those who were assigned to receive n-3 fatty acid supplementation and those who were assigned to receive placebo. (Funded by the British Heart Foundation and others; Current Controlled Trials number, ISRCTN60635500 ; ClinicalTrials.gov number, NCT00135226).

Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, Jukema JW, Lecorps G, Mahaffey KW, Moryusef A, Pordy R, Quintero K, Roe MT, Sasiela WJ, Tamby JF, Tricoci P, White HD, Zeiher AM; ODYSSEY OUTCOMES Committees and Investigators. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. N Engl J Med. 2018 Nov 29;379(22):2097-2107.

Abstract
BACKGROUND:

Patients who have had an acute coronary syndrome are at high risk for recurrent ischemic cardiovascular events. We sought to determine whether alirocumab, a human monoclonal antibody to proprotein convertase subtilisin-kexin type 9 (PCSK9), would improve cardiovascular outcomes after an acute coronary syndrome in patients receiving high-intensity statin therapy.

METHODS:
We conducted a multicenter, randomized, double-blind, placebo-controlled trial involving 18,924 patients who had an acute coronary syndrome 1 to 12 months earlier, had a low-density lipoprotein (LDL) cholesterol level of at least 70 mg per deciliter (1.8 mmol per liter), a non-high-density lipoprotein cholesterol level of at least 100 mg per deciliter (2.6 mmol per liter), or an apolipoprotein B level of at least 80 mg per deciliter, and were receiving statin therapy at a high-intensity dose or at the maximum tolerated dose. Patients were randomly assigned to receive alirocumab subcutaneously at a dose of 75 mg (9462 patients) or matching placebo (9462 patients) every 2 weeks. The dose of alirocumab was adjusted under blinded conditions to target an LDL cholesterol level of 25 to 50 mg per deciliter (0.6 to 1.3 mmol per liter). The primary end point was a composite of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization.

RESULTS:
The median duration of follow-up was 2.8 years. A composite primary end-point event occurred in 903 patients (9.5%) in the alirocumab group and in 1052 patients (11.1%) in the placebo group (hazard ratio, 0.85; 95% confidence interval [CI], 0.78 to 0.93; P<0.001). A total of 334 patients (3.5%) in the alirocumab group and 392 patients (4.1%) in the placebo group died (hazard ratio, 0.85; 95% CI, 0.73 to 0.98). The absolute benefit of alirocumab with respect to the composite primary end point was greater among patients who had a baseline LDL cholesterol level of 100 mg or more per deciliter than among patients who had a lower baseline level. The incidence of adverse events was similar in the two groups, with the exception of local injection-site reactions (3.8% in the alirocumab group vs. 2.1% in the placebo group).

CONCLUSIONS:
Among patients who had a previous acute coronary syndrome and who were receiving high-intensity statin therapy, the risk of recurrent ischemic cardiovascular events was lower among those who received alirocumab than among those who received placebo. (Funded by Sanofi and Regeneron Pharmaceuticals; ODYSSEY OUTCOMES ClinicalTrials.gov number, NCT01663402).

Manson JE, Cook NR, Lee IM, Christen W, et al. Marine n-3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer. N Engl J Med. 2019 Jan 3;380(1):23-32. doi: 10.1056/NEJMoa1811403. Epub 2018 Nov 10.

BACKGROUND:
Higher intake of marine n-3 (also called omega-3) fatty acids has been associated with reduced risks of cardiovascular disease and cancer in several observational studies. Whether supplementation with n-3 fatty acids has such effects in general populations at usual risk for these end points is unclear.

METHODS:
We conducted a randomized, placebo-controlled trial, with a two-by-two factorial design, of vitamin D3 (at a dose of 2000 IU per day) and marine n-3 fatty acids (at a dose of 1 g per day) in the primary prevention of cardiovascular disease and cancer among men 50 years of age or older and women 55 years of age or older in the United States. Primary end points were major cardiovascular events (a composite of myocardial infarction, stroke, or death from cardiovascular causes) and invasive cancer of any type. Secondary end points included individual components of the composite cardiovascular end point, the composite end

point plus coronary revascularization (expanded composite of cardiovascular events), site-specific cancers, and death from cancer. Safety was also assessed. This article reports the results of the comparison of n-3 fatty acids with placebo.

RESULTS:
A total of 25,871 participants, including 5106 black participants, underwent randomization. During a median follow-up of 5.3 years, a major cardiovascular event occurred in 386 participants in the n-3 group and in 419 in the placebo group (hazard ratio, 0.92; 95% confidence interval [CI], 0.80 to 1.06; P=0.24). Invasive cancer was diagnosed in 820 participants in the n-3 group and in 797 in the placebo group (hazard ratio, 1.03; 95% CI, 0.93 to 1.13; P=0.56). In the analyses of key secondary end points, the hazard ratios were as follows: for the expanded composite end point of cardiovascular events, 0.93 (95% CI, 0.82 to 1.04); for total myocardial infarction, 0.72 (95% CI, 0.59 to 0.90); for total stroke, 1.04 (95% CI, 0.83 to 1.31); for death from cardiovascular causes, 0.96 (95% CI, 0.76 to 1.21); and for death from cancer (341 deaths from cancer), 0.97 (95% CI, 0.79 to 1.20). In the analysis of death from any cause (978 deaths overall), the hazard ratio was 1.02 (95% CI, 0.90 to 1.15). No excess risks of bleeding or other serious adverse events were observed.

CONCLUSIONS:
Supplementation with n-3 fatty acids did not result in a lower incidence of major cardiovascular events or cancer than placebo. (Funded by the National Institutes of Health and others; VITAL ClinicalTrials.gov number, NCT01169259 .).

Appendix 3: Medline Search Strategy
Database: Ovid MEDLINE(R) <2016 to February Week 4 2019>
Search Strategy:
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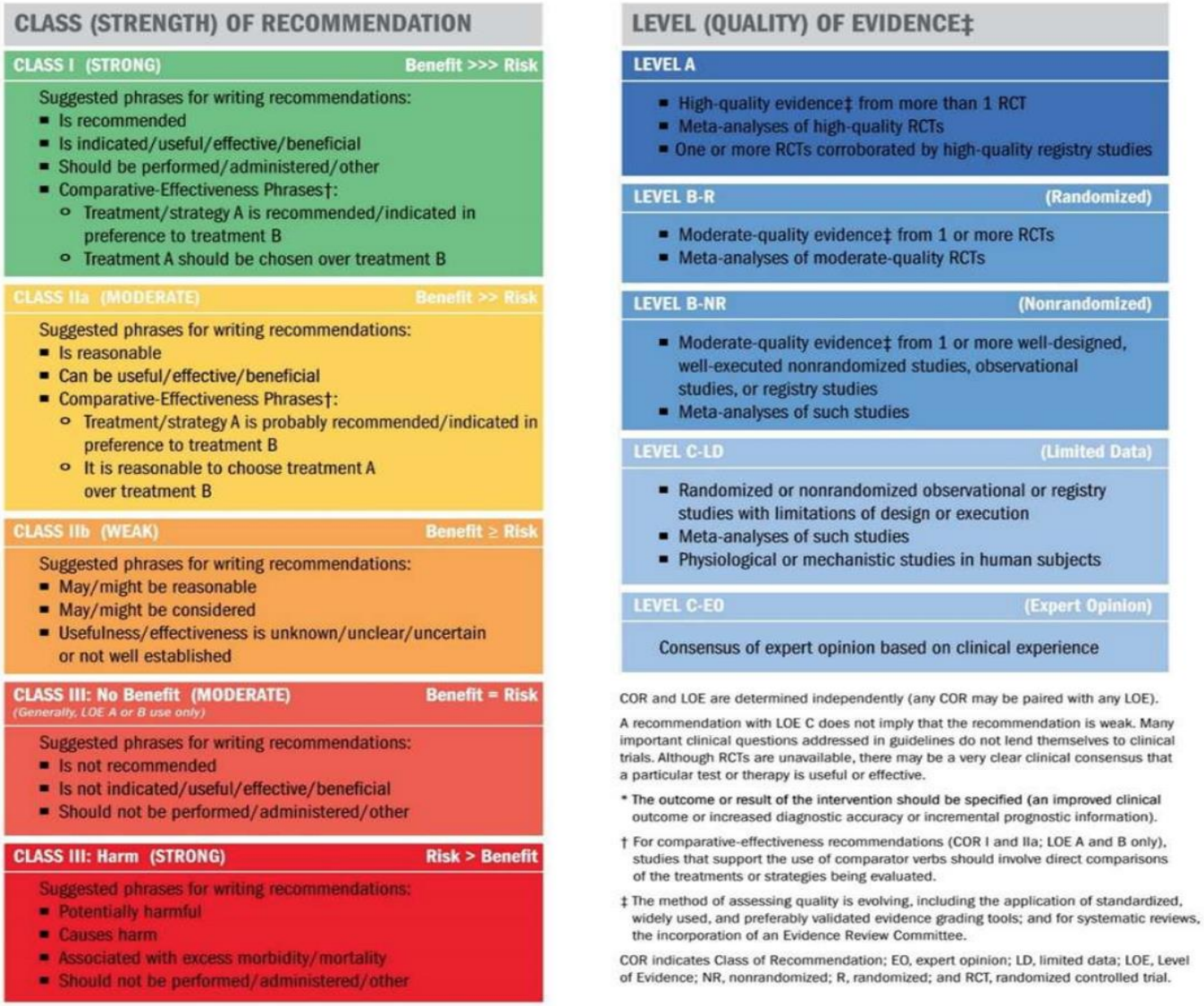
1 (Cholestyramine Resin or Colesevelam Hydrochloride or Colestipol or Docosahexaenoic Acids or Eicosapentaenoic acid or ezetimibe or ezetimibe, simvastatin drug combination or Fatty acids, Omega-3 or Fenofibrate or Fenofibrate micronized or Gemfibrozil or Inositol or Icosapent ethyl or Fenofibric acid or Niacin or Nicotinamide or Nicotinic acid or Lovaza or Bile acid sequestrants or Statin, high-intensity or Lomitapide or Mipomersen or alirocumab or evolocumab or psck9 inhibitors).af. (106523)
2 (Coronary Artery Disease or Coronary Disease or Dyslipidemia or Dyslipidemias or Hypertriglyceridemias or Myocardial Infarction or Stroke or Cardiovascular Disease or Cardiovascular Diseases).af. (844491)
3 ((Cholestyramine Resin or Colesevelam Hydrochloride or Colestipol or Docosahexaenoic Acids or Eicosapentaenoic acid or ezetimibe or ezetimibe, simvastatin drug combination or Fatty acids, Omega-3 or Fenofibrate or Fenofibrate micronized or Gemfibrozil or Inositol or Icosapent ethyl or Fenofibric acid or Niacin or Nicotinamide or Nicotinic acid or Lovaza or Bile acid sequestrants or Statin, high-intensity or Lomitapide or Mipomersen or alirocumab or evolocumab or psck9 inhibitors) and (Coronary Artery Disease or Coronary Disease or Dyslipidemia or Dyslipidemias or Hypertriglyceridemias or Myocardial Infarction or Stroke or Cardiovascular Disease or Cardiovascular Diseases)).af. (8963)
4 limit 3 to (english language and humans) (6967)
5 limit 4 to (english language and humans and yr="2016 -Current" and (clinical trial, all or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review" or systematic reviews as topic) and (in process or medline)) (339)

Appendix 4: Key Inclusion Criteria

Population	Patients with cardiovascular disease or at high risk for cardiovascular disease
Intervention	Pharmacotherapy listed in Appendix 1
Comparator	Pharmacotherapy listed in Appendix 1 or placebo
Outcomes	Quality of life Morbidity Mortality Major CV events (CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization) Serious Adverse Events Discontinuation from Serious Adverse Events
Timing	Any study duration; literature search from January 2016 through March 1st 2019
Setting	Outpatient

Appendix 5: 2018 Cholesterol Guidelines Class of Recommendation and Level of Evidence Descriptions



CLASS (STRENGTH) OF RECOMMENDATION

CLASS I (STRONG) — **Benefit >>> Risk**

Suggested phrases for writing recommendations:
- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

CLASS IIa (MODERATE) — **Benefit >> Risk**

Suggested phrases for writing recommendations:
- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

CLASS IIb (WEAK) — **Benefit ≥ Risk**

Suggested phrases for writing recommendations:
- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well established

CLASS III: No Benefit (MODERATE) — **Benefit = Risk**
(Generally, LOE A or B use only)

Suggested phrases for writing recommendations:
- Is not recommended
- Is not indicated/useful/effective/beneficial
- Should not be performed/administered/other

CLASS III: Harm (STRONG) — **Risk > Benefit**

Suggested phrases for writing recommendations:
- Potentially harmful
- Causes harm
- Associated with excess morbidity/mortality
- Should not be performed/administered/other

LEVEL (QUALITY) OF EVIDENCE‡

LEVEL A
- High-quality evidence‡ from more than 1 RCT
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

LEVEL B-R (Randomized)
- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

LEVEL B-NR (Nonrandomized)
- Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
- Meta-analyses of such studies

LEVEL C-LD (Limited Data)
- Randomized or nonrandomized observational or registry studies with limitations of design or execution
- Meta-analyses of such studies
- Physiological or mechanistic studies in human subjects

LEVEL C-EO (Expert Opinion)

Consensus of expert opinion based on clinical experience

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR I and IIa; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

PCSK9 Inhibitors

Goal(s):

- ~~To provide PSCK9 inhibitor coverage only for funded diagnoses supported by the medical literature.~~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 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	

3. Does the patient have very high-risk clinical atherosclerotic cardiovascular disease (ASCVD), defined as documented history of ≥1 of the following: 4. Myocardial infarction; OR 5. Unstable angina; OR 6. Coronary revascularization procedure (PCI or CABG); OR 7. Symptomatic peripheral artery disease; OR 8. Non-hemorrhagic stroke; 4. **5. AND** 6.3. At least 1 major risk factor or at least 2 minor risk factors below (if the patient has a combination of ≥2 of the above diagnoses, they do not need an additional risk factor to qualify):multiple major ASCVD events **OR** one major ASCVD event and multiple high-risk conditions (See below) Major risk factors (1 required):ASCVD events • DiabetesRecent ACS (within past 12 months) • History of MI (other than recent ACS from above) • History of ischemic stroke • Symptomatic peripheral artery disease • Age ≥ 65 years • MI or non-hemorrhagic stroke within the last 6 months • Current daily cigarette smoking Minor risk factors (2 required):High-Risk Conditions: • Age ≥ 65history of non-MI related coronary revascularization •	**Yes:** Go to #4	**No:** Go to #7

Approval Criteria		
• Heterozygous familial hypercholesterolemia~~residual coronary artery disease with ≥ 40% stenosis in ≥ 2 large vessels~~ • • History of prior CABG or PCI~~Most recent HDL-C < 40 mg/dL for men and < 50 mg/dL for women~~ • • Diabetes Mellitus~~Most recent hsCRP > 2.0 mg/L~~ • • Hypertension~~Most recent LDL-C ≥ 130 mg/dLor non-HDL-C ≥ 160 mg/dL~~ • • Chronic Kidney Disease~~metabolic syndrome~~ • Current smoking • Persistently elevated LDL-C ≥ 100 despite maximally tolerated statin therapy and ezetimibe • History of congestive heart failure		

Approval Criteria		
~~7.~~4. Has the patient taken a daily high-intensity statin table below) and ezetimibe 10 mg daily for at least 3 months with ~~<50% LDL-C reduction~~a LDL-C still ≥ 70 mg/dl or non-HDL ≥ 100 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
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? 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~~Go to #7~~

Approval Criteria		
7. Does the patient have a diagnosis of homozygous or heterozygous familial hypercholesterolemia? Note: Prescriber must provide chart documentation of diagnosis and recent LDL-C (within last 12 weeks).	**Yes:** Go to #8	**No:** Pass to RPh; deny for medical appropriateness.
8. Does the patient still have a LDL-C of ≥ 100 mg/dl while taking ~~already takes~~ a maximally tolerated statin and~~/or~~ 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	
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. ~~Stone NJ, et al. 2013 ACC/AHA Blood Cholesterol Guideline.~~

High-intensity Statins (≥50% LDL-C Reduction)	Moderate-intensity Statins (30 to <50% LDL-C Reduction)	
Atorvastatin 40-80 mg Rosuvastatin 20-40 mg ~~Rosuvastatin 20-40 mg~~	Atorvastatin 10-20 mg Fluvastatin 80 mg Lovastatin 40-80 mg	Pitavastatin 1~~2~~-4 mg Pravastatin 40-80 mg Simvastatin 20-40 mg Rosuvastatin 5-10 mg

~~References:~~
~~1. NICE Clinical Guideline 181. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. Available at: guidance.nice.org.uk/cg181. Accessed 18 September 2015.~~
~~2. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;129(25 Suppl 2):S1-45. doi: 10.1161/01.cir.0000437738.63853.7a.~~

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

Mipomersen and Lomitapide

Goal(s):

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

Length of Authorization:

- Up to 6 months

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the drug prescribed by or in consultation with a specialist in lipid disorders?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis homozygous familial hypercholesterolemia?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Has the patient tried and failed or does the patient have a medical contraindication to maximum lipid lowering therapy with a combination of traditional drugs (high-intensity statin with ezetimibe (see Table 1)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
5. Has the patient failed or are they not appropriate for LDL-C apheresis; **OR** is LDL-C apheresis not available?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Table 1. High-intensity Statins.

High-intensity Statins (≥50% LDL-C Reduction)	
Atorvastatin 40-80 mg	Rosuvastatin 20-40 mg

Ref. Stone NJ, et al. 2013 ACC/AHA Blood Cholesterol Guideline.

P&T/DUR Review: *5/19 (MH); 11/16 (DM); 5/16; 9/13; 7/13; 5/13*
Implementation: *1/1/17; 1/1/14; 11/21/2013*

Omega-3 Fatty Acids

Goal(s):

- Restrict use of omega-3 fatty acids to patients at increased risk for pancreatitis.

Length of Authorization:

- Up to 12 months

Requires PA:

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

Covered Alternatives:

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

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

Approval Criteria		
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:** Pass to RPh. Deny; medical appropriateness.
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).

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

P&T/DUR Review: *5/19 (MH); 11/16 (DM); 3/14*
Implementation: *1/1/17; 5/1/14*