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, July 25th, 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 in accordance with Oregon Revised Statute 183.333.

I. CALL TO ORDER

1:00 PM	A. Roll Call & Introductions	R. Citron (OSU)
	B. Conflict of Interest Declaration	R. Citron (OSU)
	C. Approval of Agenda and Minutes	R. Citron (OSU)
	D. Department Update	T. Douglass (OHA)
	E. Legislative Update	T. Douglass (OHA)
1:15 PM	II. CONSENT AGENDA TOPICS	Chair
	A. Quarterly Utilization Reports	
	B. CMS Annual Report	
	C. Beta-agonists, inhaled short-acting	
	1. Public Comment	

II. 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. Non-statin Low-Density Lipoprotein Cholesterol (LDL-C) Lowering Therapy and Cardiovascular Outcomes	
	2. Update on Medications Used to Manage Opioid Use Disorder and Opioid Withdrawal	

III. DUR NEW BUSINESS

1:30 PM	A. Opioid/Sedative Retrospective DUR Proposal	S. Servid (OSU)
	1. Drug Use Evaluation	D. Engen (OSU)
	2. Retrospective DUR Proposal/Provider Education	
	3. Public Comment	
	4. Discussion of Clinical Recommendations to OHA	

IV. PREFERRED DRUG LIST NEW BUSINESS

1:50 PM	A. Antidepressant Class Update and New Drug Evaluation 1. Class Update 2. Spravato™ (esketamine) New Drug Evaluation/Safety Edit 3. Zulresso™ (brexanolone) New Drug Evaluation/Safety Edit 4. Public Comment 5. Discussion of Clinical Recommendations to OHA	K. Sentena (OSU)
2:15 PM	B. Transthyretin Mediated Amyloidosis New Drug Evaluations 1. Onpattro™ (patisiran) New Drug Evaluation 2. Tegsedi™ (inotersen) New Drug Evaluation 3. Prior Authorization Criteria 4. Public Comment 5. Discussion of Clinical Recommendations to OHA	M. Herink (OSU)
2:35 PM	C. Atopic Dermatitis Class Update and Dupilumab Drug Update 1. Class Update/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	D. Moretz (OSU)
2:55 PM	BREAK	
3:05 PM	D. Narcolepsy Agents DERP Summary and New Drug Evaluation 1. Xyrem® (sodium oxybate) Drug Review 2. Sunosi™ (solriamfetol) New Drug Evaluation/Safety Edit 3. Modafinil & Armodafinil DERP Summary /Safety Edit 4. Public Comment 5. Discussion of Clinical Recommendations to OHA	S. Servid (OSU)
3:30 PM	E. Bone Metabolism Class Update and New Drug Evaluation 1. Class Update/Prior Authorization Criteria 2. Evenity™ (romosozumab-aqqg) New Drug Evaluation 3. Public Comment 4. Discussion of Clinical Recommendations to OHA	D. Moretz (OSU)
3:50 PM	F. Aemcolo™ (rifamycin) New Drug Evaluation 1. New Drug Evaluation/Prior Authorization 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	D. Moretz (OSU)
4:05 PM	V. EXECUTIVE SESSION	
4:50 PM	VI. RECONVENE for PUBLIC RECOMMENDATIONS 1. Public Comment 2. Financial Recommendations to OHA	
	VII. 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, May 23, 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 in accordance with Oregon Revised Statute 183.333

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

Members Present by Phone: Kelley Burnett, DO; David Pass, MD**;** Stacy Ramirez, PharmD; James Slater, PharmD

Staff Present: Roger Citron, RPh; David Engen, PharmD; Richard Holsapple, RPh; Deanna Moretz, PharmD; Kathy Sentena, PharmD; Sarah Servid, PharmD; Renae Wentz, MD; Dee Weston; Trevor Douglass, DC, MPH; Brandon Wells; Jennifer Torkelson; Michelle Hatfield; Joelle Ayoub, PharmD

Staff Present by Phone:

Audience: Rick Frees, Vertex; Tim McFerrin, Alkermes; Roy Lindfield; Craig Sexton, GSK; *Anthony Wheeler, Lilly; Rebecca Cashner, OSU/OHSU COP; Venus Holder, Lilly; Jeremy Strand, Alexion; Melanie Lamarche, Merck; Geetika Gupta, Merck; Lisa Boyle, WVP Health; Steve Isaki, Lundbeck; Mae Kwong, Janssen; Doug Buriani, SOBI; Maggi Olmon, AbbVie; Donna Tehrani; Mayra Barrera; Laura Jeffcoat, AbbVie; Danielle Shannon, WVP Health; *Maria Agapova, Teva; Diann Matthews, Merz; Christian Johnson

(*) Provided verbal testimony

Written testimony provided: Posted to OSU Website

I. CALL TO ORDER

A. Roll Call & Introductions
B. Conflict of Interest Declaration
C. Approval of Agenda and Minutes
ACTION: Motion to approve, 2nd, all in favor
D. Department Update: Trevor Douglass, staffing updates
E. Legislative Update: Trevor Douglass reviewed agency policy during legislative session regarding discussion of active bills. Reviewed: HB2692- passed & signed, HB2678 to Ways & Means, and HB3397

II. CONSENT AGENDA TOPICS

A. Quarterly Utilization Reports
ACTION: Motion to approve, 2nd, all in favor

III. DUR ACTIVIES

A. ProDUR Report - Mr. Holsapple presented the ProDUR report
B. RetroDUR Report - Dr. Engen presented the RetroDUR report
C. Oregon State Drug Reviews
1. 2017-2018 Year in Review: Important Safety Updates
2. Benzodiazepine Safety and Tapering
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 1:35 PM

A. GnRH Modifiers
Mr. Citron presented the proposal to:
1. Add the class to the PMPDP and designate all agents as non-preferred

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

B. Combination Biologic Therapy Drug Use Evaluation
Dr. Servid presented the proposal to:
1. Update PA criteria to include a maximum dose for patients with rheumatoid arthritis prescribed tofacitinib and to reinforce periodic tuberculosis testing

ACTION: Update Renewal criteria #3 to reference prescribing provider rather than prescribing physician and develop a RetroDUR provider education on DMARD adherence after 3 months
Motion to approve, 2nd, all in favor

V. DUR NEW BUSINESS

A. Attention Deficit Hyperactivity Disorder Drug Use Evaluation
Dr. Ayoub presented the proposal to:
1. Continue to monitor use of ADHD medications
2. 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

Action: Develop RetroDUR to evaluate combination of stimulant and antipsychotic medications
Motion to approve, 2nd all in favor

B. Adherence Monitoring in Schizophrenia Patients
Dr. Servid presented the proposal to:
1. Recommend implementation of a retrospective initiative to notify providers when patients on routine therapy for schizophrenia miss a medication refill

ACTION: Modify proposed letter to streamline message and explore transitions of care opportunities for patients with denials based on lost Medicaid eligibility
Motion to approve, 2nd all in favor

VI. PREFERRED DRUG LIST NEW BUSINESS

A. Asthma/COPD Class Update and New Drug Evaluation
Dr. Sentena presented the proposal to:
1. Recommend clerical revisions to prior authorization (PA) criteria to remove references to guideline classifications of COPD
2. Evaluate costs in executive session

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

B. Migraine Treatment and Prevention DERP Summary
Dr. Sentena presented the proposal to:
1. No changes to the PDL are recommended based on review of the evidence
2. Evaluate costs in executive session

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

C. CGRP Inhibitors DERP Summary
Dr. Engen presented the proposal to:

1. No changes to the PDL are recommended based on review of the evidence
2. Evaluate costs in executive session

ACTION: Change duration of approval for renewal criteria to 6 months
Motion to approve, 2nd, all in favor

D. Potassium Exchangers Class Update and New Drug Evaluation
Dr. Moretz presented the proposal to:
1. Add sodium zirconium cyclosilicate to patiromer PA criteria to insure appropriate utilization for FDA-approved indications
2. Remove requirement for trial and failure of kayexlate because of the acute indication for kayexlate and black box warning
3. Evaluate costs in executive session

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

E. Other Dyslipidemia Drugs Class Update
Dr. Herink presented the proposal to:
1. Update PA criteria to be consistent with the new evidence for use of non-statins to prevent ASCVD events
2. Consider retiring the PA criteria for lomitapide and mipomersen due to no utilization
3. Make gemfibrozil non-preferred due to safety concerns with use in combination with statin therapy
4. 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; William Origer, MD; Cathy Zehrung, RPh

Members Present by Phone: Stacy Ramirez, PharmD; James Slater, PharmD; David Pass, MD

Staff Present: Roger Citron, RPh; David Engen, PharmD, CGP; Richard Holsapple, RPh; Deanna Moretz, PharmD; Kathy Sentena, PharmD; Sarah Servid, PharmD; Renae Wentz, MD; Trevor Douglass, DC, MPH; Brandon Wells; Jennifer Torkelson; Michelle Hatfield; Joelle Ayoub

VIII. RECONVENE for PUBLIC RECOMMENDATIONS

A. Asthma/COPD Class Update and New Drug Evaluation
Recommendation: **Make Dulera, Tudorza, and Asmanex to preferred**

ACTION: Motion to approve, 2nd all in favor

B. Migraine Treatment and Prevention DERP Summary
Recommendation: **Make sumatriptan succinate syringe and zolmitriptan tablets, rapid tablets and nasal spray preferred**

ACTION: Motion to approve, 2nd all in favor

C. CGRP Inhibitors DERP Summary
Recommendation: **Make all agents in the class non-preferred**

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

D. Potassium Exchangers Class Update and New Drug Evaluation
Recommendation: **Make patiromer and maintain sodium zirconium cyclosilicate as non-preferred**

ACTION: Motion to approve, 2nd all in favor

E. Other Dyslipidemia Drugs Class Update
Recommendation: **Make ezetimibe and evolocumab preferred**

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

X. ADJOURN

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Pharmacy Utilization Summary Report: January 2018 - December 2018

Eligibility	Jan-18	Feb-18	Mar-18	Apr-18	May-18	Jun-18	Jul-18	Aug-18	Sep-18	Oct-18	Nov-18	Dec-18	Avg Monthly
Total Members (FFS & Encounter)	961,458	959,824	963,504	965,503	964,592	965,132	962,205	964,077	963,131	964,428	966,366	965,956	963,848
FFS Members	121,061	121,425	120,975	121,038	113,512	117,714	120,682	119,156	121,522	115,577	120,900	125,681	119,937
OHP Basic with Medicare	33,777	34,033	34,222	34,378	34,471	34,742	34,887	35,039	35,293	35,249	35,494	35,531	34,760
OHP Basic without Medicare	12,068	12,220	12,198	12,207	11,665	11,817	11,917	11,827	11,956	11,702	11,714	11,824	11,926
ACA	75,216	75,172	74,555	74,453	67,376	71,155	73,878	72,290	74,273	68,626	73,692	78,326	73,251
Encounter Members	840,397	838,399	842,529	844,465	851,080	847,418	841,523	844,921	841,609	848,851	845,466	840,275	843,911
OHP Basic with Medicare	41,156	41,089	41,117	41,143	41,324	41,337	41,300	41,375	41,334	41,471	41,476	41,372	41,291
OHP Basic without Medicare	63,767	63,431	63,435	63,126	63,424	63,149	62,869	62,744	62,264	62,281	62,113	61,913	62,876
ACA	735,474	733,879	737,977	740,196	746,332	742,932	737,354	740,802	738,011	745,099	741,877	736,990	739,744

Gross Cost Figures for Drugs	Jan-18	Feb-18	Mar-18	Apr-18	May-18	Jun-18	Jul-18	Aug-18	Sep-18	Oct-18	Nov-18	Dec-18	YTD Sum
Total Amount Paid (FFS & Encounter)	$79,187,903	$69,822,456	$77,861,750	$74,838,208	$77,858,208	$73,224,369	$74,411,276	$78,398,476	$69,133,337	$79,373,733	$73,730,674	$70,606,508	$898,446,898
Mental Health Carve-Out Drugs	$7,925,947	$7,114,854	$7,700,187	$7,636,429	$7,949,635	$7,574,582	$7,683,569	$7,929,716	$7,132,763	$8,142,288	$7,651,758	$7,528,997	$91,970,726
OHP Basic with Medicare	$2,895	$73	$2,609	$1,634	$56	$39	$4,450	$6,085	$4,293	$5,584	$4,637	$5,486	$37,841
OHP Basic without Medicare	$3,288,120	$3,031,375	$3,241,144	$3,203,253	$3,345,129	$3,221,481	$3,199,452	$3,339,301	$2,945,714	$3,385,752	$3,133,502	$3,114,151	$38,448,375
ACA	$4,579,923	$4,029,579	$4,405,932	$4,376,040	$4,552,089	$4,301,238	$4,425,609	$4,521,954	$4,131,281	$4,694,738	$4,452,812	$4,355,827	$52,827,019
FFS Physical Health Drugs	$3,521,481	$2,970,054	$3,006,645	$2,905,123	$2,996,948	$2,743,627	$2,795,209	$3,070,619	$2,496,162	$3,066,009	$2,654,890	$2,672,517	$34,899,285
OHP Basic with Medicare	$261,261	$237,428	$251,587	$240,637	$274,483	$227,045	$228,266	$237,153	$213,497	$291,728	$244,046	$240,575	$2,947,705
OHP Basic without Medicare	$1,255,848	$950,195	$933,916	$932,800	$1,010,685	$855,937	$822,590	$962,048	$717,432	$936,471	$814,379	$780,306	$10,972,606
ACA	$1,869,024	$1,644,682	$1,681,910	$1,581,508	$1,573,087	$1,529,070	$1,612,083	$1,703,599	$1,443,381	$1,712,327	$1,466,823	$1,527,747	$19,345,242
FFS Physician Administered Drugs	$1,697,066	$1,618,066	$1,473,395	$1,515,670	$1,669,039	$1,667,838	$1,493,406	$1,712,874	$1,437,802	$1,840,044	$1,520,490	$1,294,577	$18,940,268
OHP Basic with Medicare	$422,612	$376,273	$419,053	$425,716	$484,206	$429,176	$346,591	$452,583	$418,608	$430,336	$461,728	$306,624	$4,973,505
OHP Basic without Medicare	$295,625	$488,847	$277,513	$104,619	$306,643	$388,840	$275,453	$386,310	$217,255	$599,706	$133,827	$119,729	$3,594,366
ACA	$685,465	$491,531	$508,596	$403,809	$512,426	$482,970	$500,477	$564,399	$493,960	$464,017	$573,806	$541,549	$6,223,005
Encounter Physical Health Drugs	$54,108,265	$48,004,340	$54,557,472	$51,490,822	$53,595,181	$50,460,774	$50,279,946	$53,185,825	$47,490,933	$54,168,914	$50,015,579	$48,428,142	$615,786,194
OHP Basic with Medicare	$155,475	$138,309	$154,989	$116,892	$132,320	$126,453	$190,485	$271,568	$228,474	$263,063	$235,808	$248,346	$2,262,181
OHP Basic without Medicare	$13,935,596	$12,377,264	$14,267,710	$13,405,801	$13,919,949	$13,290,529	$13,362,823	$14,029,663	$12,446,471	$14,205,170	$13,152,879	$12,797,657	$161,191,512
ACA	$39,249,825	$34,805,825	$39,397,750	$37,241,558	$38,824,036	$36,426,655	$36,107,766	$38,207,305	$34,139,714	$39,059,592	$36,005,446	$34,800,596	$444,266,068
Encounter Physician Administered Drugs	$11,935,143	$10,115,142	$11,124,051	$11,290,164	$11,647,405	$10,777,547	$12,159,146	$12,499,443	$10,575,677	$12,156,478	$11,887,956	$10,682,275	$136,850,425
OHP Basic with Medicare	$278,862	$233,763	$285,711	$260,172	$256,245	$234,794	$260,378	$253,430	$219,859	$279,305	$273,029	$224,616	$3,060,165
OHP Basic without Medicare	$2,967,899	$2,260,643	$2,436,957	$2,722,966	$2,705,146	$2,272,587	$2,988,811	$2,829,624	$2,547,278	$2,782,709	$2,728,306	$2,446,870	$31,689,795
ACA	$8,532,389	$7,505,318	$8,255,836	$8,126,331	$8,536,834	$8,142,874	$8,658,060	$9,288,516	$7,684,030	$8,903,901	$8,760,419	$7,874,044	$100,268,550

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

Last Updated: July 18, 2019

Drug Use Research & Management Program
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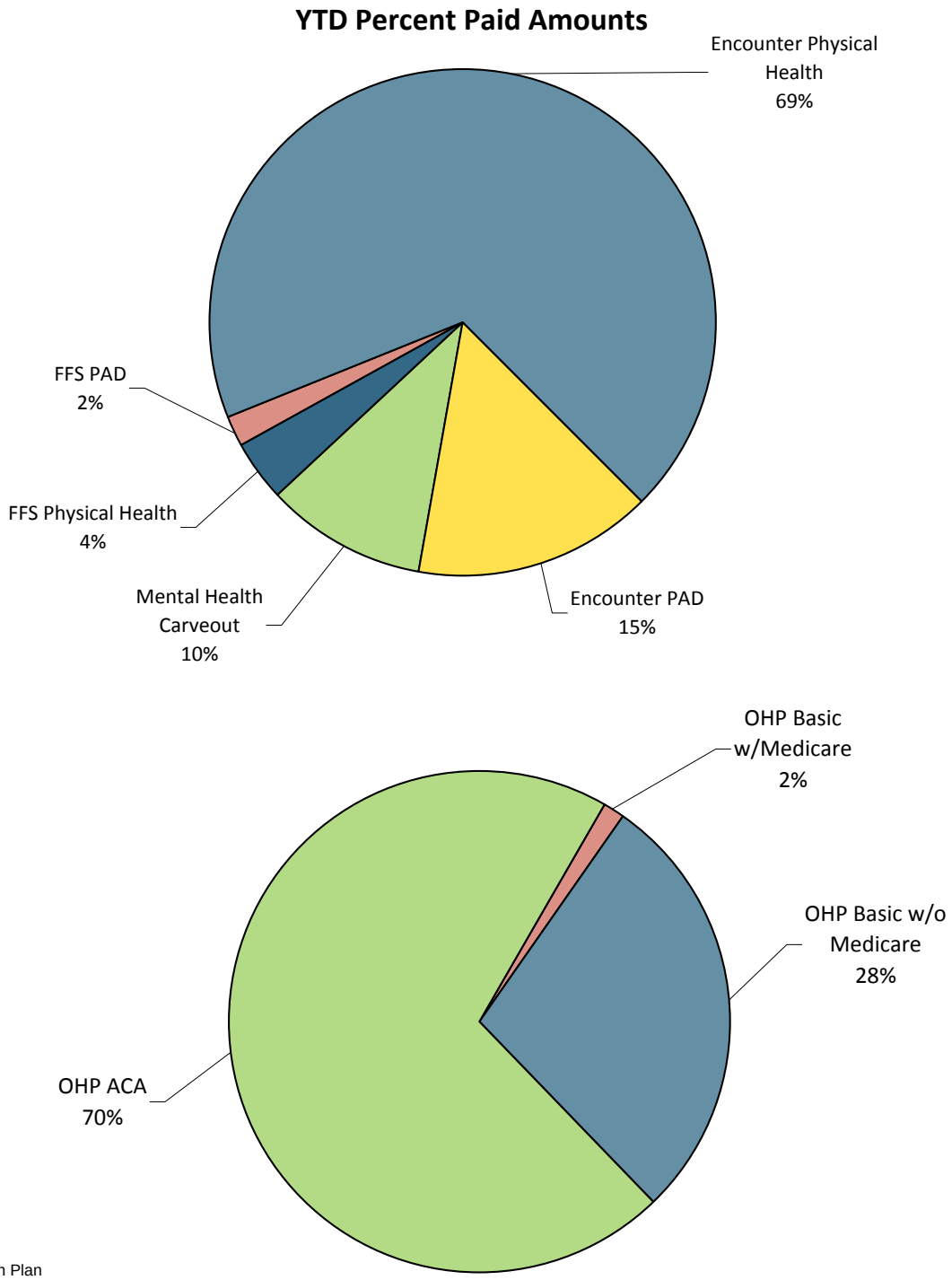
Pharmacy Utilization Summary Report: January 2018 - December 2018



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

Last Updated: July 18, 2019

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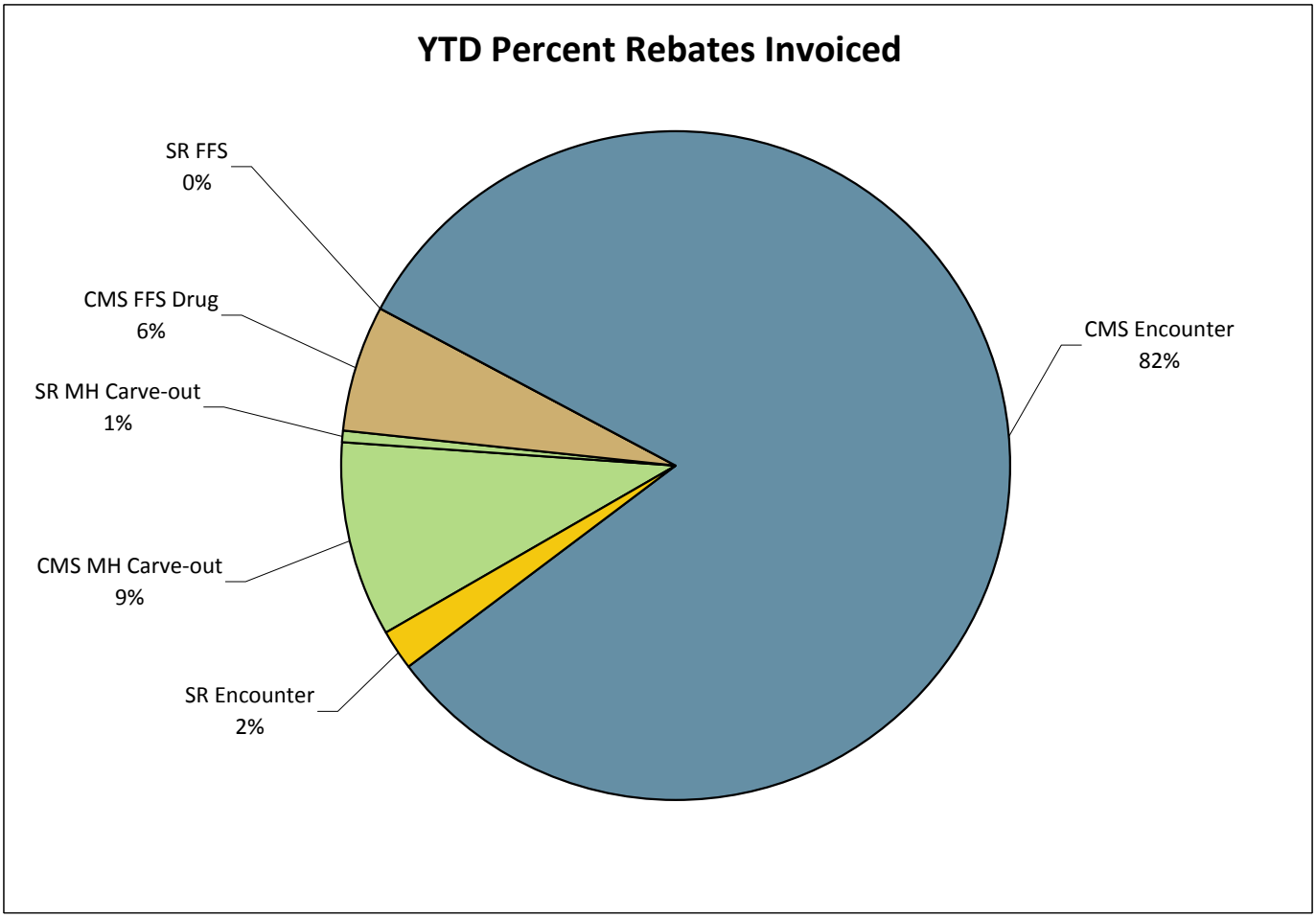
Pharmacy Utilization Summary Report: January 2018 - December 2018

Quarterly Rebates Invoiced	2018-Q1	2018-Q2	2018-Q3	2018-Q4	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$108,482,752	$106,512,652	$103,705,653	$99,690,097	$418,391,155
CMS MH Carve-out	$9,692,392	$9,878,905	$9,904,362	$10,155,055	$39,630,714
SR MH Carve-out	$533,658	$559,564	$573,570	$654,824	$2,321,616
CMS FFS Drug	$6,889,112	$6,419,025	$6,166,710	$5,458,772	$24,933,618
SR FFS	$213,826	$201,081	$213,713	$210,186	$838,807
CMS Encounter	$89,233,528	$87,615,620	$84,211,213	$81,306,511	$342,366,871
SR Encounter	$1,920,236	$1,838,458	$2,636,086	$1,904,748	$8,299,528

Quaterly Net Drug Costs	2018-Q1	2018-Q2	2018-Q3	2018-Q4	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$118,389,357	$119,408,133	$118,237,435	$124,020,818	$480,055,744
Mental Health Carve-Out Drugs	$12,514,938	$12,722,178	$12,268,117	$12,513,164	$50,018,396
FFS Phys Health + PAD	$7,183,769	$6,878,140	$6,625,649	$7,379,570	$28,067,128
Encounter Phys Health + PAD	$98,690,649	$99,807,815	$99,343,670	$104,128,085	$401,970,219



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

Last Updated: July 18, 2019

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Pharmacy Utilization Summary Report: January 2018 - December 2018

Gross PMPM Drug Costs (Rebates not Subtracted)	Jan-18	Feb-18	Mar-18	Apr-18	May-18	Jun-18	Jul-18	Aug-18	Sep-18	Oct-18	Nov-18	Dec-18	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$82.36	$72.75	$80.81	$77.51	$80.72	$75.87	$77.33	$81.32	$71.78	$82.30	$76.30	$73.09	$77.68
Mental Health Carve-Out Drugs	$8.24	$7.41	$7.99	$7.91	$8.24	$7.85	$7.99	$8.23	$7.41	$8.44	$7.92	$7.79	$7.95
FFS Physical Health Drugs	$29.09	$24.46	$24.85	$24.00	$26.40	$23.31	$23.16	$25.77	$20.54	$26.53	$21.96	$21.26	$24.28
FFS Physician Administered Drugs	$14.02	$13.33	$12.18	$12.52	$14.70	$14.17	$12.37	$14.38	$11.83	$15.92	$12.58	$10.30	$13.19
Encounter Physical Health Drugs	$64.38	$57.26	$64.75	$60.97	$62.97	$59.55	$59.75	$62.95	$56.43	$63.81	$59.16	$57.63	$60.80
Encounter Physician Administered Drugs	$14.20	$12.06	$13.20	$13.37	$13.69	$12.72	$14.45	$14.79	$12.57	$14.32	$14.06	$12.71	$13.51

Claim Counts	Jan-18	Feb-18	Mar-18	Apr-18	May-18	Jun-18	Jul-18	Aug-18	Sep-18	Oct-18	Nov-18	Dec-18	Avg Monthly
Total Claim Count (FFS & Encounter)	1,094,674	955,495	1,061,968	1,034,386	1,073,385	1,005,678	1,005,398	1,038,531	962,005	1,071,590	1,005,253	989,852	1,024,851
Mental Health Carve-Out Drugs	159,755	141,766	155,512	153,724	159,272	149,545	152,753	157,436	144,480	161,680	152,564	150,616	153,259
FFS Physical Health Drugs	66,824	59,132	61,715	59,107	59,972	56,136	55,353	57,619	52,379	58,474	54,843	53,666	57,935
FFS Physician Administered Drugs	17,685	14,465	15,250	14,394	15,233	14,270	14,787	15,574	14,025	14,911	13,339	13,469	14,784
Encounter Physical Health Drugs	738,784	643,788	721,200	700,671	727,504	680,744	674,508	697,536	648,578	723,933	679,631	668,594	692,123
Encounter Physician Administered Drugs	111,626	96,344	108,291	106,490	111,404	104,983	107,997	110,366	102,543	112,592	104,876	103,507	106,752

Gross Amount Paid per Claim (Rebates not Subtracted)	Jan-18	Feb-18	Mar-18	Apr-18	May-18	Jun-18	Jul-18	Aug-18	Sep-18	Oct-18	Nov-18	Dec-18	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$72.34	$73.07	$73.32	$72.35	$72.54	$72.81	$74.01	$75.49	$71.86	$74.07	$73.35	$71.33	$73.05
Mental Health Carve-Out Drugs	$49.61	$50.19	$49.52	$49.68	$49.91	$50.65	$50.30	$50.37	$49.37	$50.36	$50.15	$49.99	$50.01
FFS Physical Health Drugs	$52.70	$50.23	$48.72	$49.15	$49.97	$48.87	$50.50	$53.29	$47.66	$52.43	$48.41	$49.80	$50.14
FFS Physician Administered Drugs	$95.96	$111.86	$96.62	$105.30	$109.57	$116.88	$100.99	$109.98	$102.52	$123.40	$113.99	$96.12	$106.93
Encounter Physical Health Drugs	$73.24	$74.57	$75.65	$73.49	$73.67	$74.13	$74.54	$76.25	$73.22	$74.83	$73.59	$72.43	$74.13
Encounter Physician Administered Drugs	$106.92	$104.99	$102.72	$106.02	$104.55	$102.66	$112.59	$113.25	$103.13	$107.97	$113.35	$103.20	$106.78

Gross Amount Paid per Claim - Generic-Multi Source Drugs (Rebates not Subtracted)	Jan-18	Feb-18	Mar-18	Apr-18	May-18	Jun-18	Jul-18	Aug-18	Sep-18	Oct-18	Nov-18	Dec-18	Avg Monthly
Generic-Multi Source Drugs: Average Paid / Claim (FFS & Encounter)	$20.48	$19.94	$19.68	$19.46	$19.34	$19.21	$19.10	$19.09	$18.81	$18.26	$18.03	$18.08	$19.12
Mental Health Carve-Out Drugs	$21.85	$22.03	$21.24	$20.71	$20.80	$20.91	$20.96	$20.77	$19.38	$19.53	$19.50	$18.47	$20.51
FFS Physical Health Drugs	$18.08	$17.74	$17.22	$16.46	$16.49	$16.46	$16.27	$16.21	$16.16	$16.43	$16.67	$15.90	$16.67
Encounter Physical Health Drugs	$20.32	$19.58	$19.47	$19.36	$19.18	$18.98	$18.81	$18.86	$18.84	$18.06	$17.74	$18.13	$18.94

0

Gross Amount Paid per Claim - Branded-Single Source Drugs (Rebates not Subtracted)	Jan-18	Feb-18	Mar-18	Apr-18	May-18	Jun-18	Jul-18	Aug-18	Sep-18	Oct-18	Nov-18	Dec-18	Avg Monthly
Branded-Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$324.73	$341.66	$350.64	$342.89	$348.54	$349.02	$360.09	$361.53	$337.92	$348.22	$356.52	$356.65	$348.20
Mental Health Carve-Out Drugs	$948.18	$984.91	$974.52	$993.64	$989.73	$1,011.82	$998.88	$994.10	$1,004.42	$1,017.15	$1,014.13	$1,021.73	$996.10
FFS Physical Health Drugs	$143.32	$139.09	$135.01	$137.70	$140.90	$136.71	$144.87	$152.16	$132.89	$152.25	$141.60	$149.45	$142.16
Encounter Physical Health Drugs	$327.60	$346.66	$356.30	$345.40	$350.90	$351.12	$362.31	$363.79	$337.61	$345.78	$355.66	$353.65	$349.73

0

Generic Drug Use Percentage	Jan-18	Feb-18	Mar-18	Apr-18	May-18	Jun-18	Jul-18	Aug-18	Sep-18	Oct-18	Nov-18	Dec-18	Avg Monthly
Generic Drug Use Percentage	84.4%	84.8%	84.9%	85.0%	85.2%	85.0%	85.4%	85.0%	84.7%	84.5%	85.2%	85.5%	85.0%
Mental Health Carve-Out Drugs	97.0%	97.1%	97.0%	97.0%	97.0%	97.0%	97.0%	97.0%	97.0%	96.9%	96.9%	96.9%	97.0%
FFS Physical Health Drugs	72.4%	73.2%	73.3%	73.0%	73.1%	73.0%	73.4%	72.7%	73.0%	73.5%	74.6%	74.6%	73.3%
Encounter Physical Health Drugs	82.8%	83.2%	83.3%	83.4%	83.6%	83.4%	83.8%	83.4%	82.9%	82.7%	83.5%	83.8%	83.3%

Preferred Drug Use Percentage	Jan-18	Feb-18	Mar-18	Apr-18	May-18	Jun-18	Jul-18	Aug-18	Sep-18	Oct-18	Nov-18	Dec-18	Avg Monthly
Preferred Drug Use Percentage	87.09%	86.96%	86.86%	86.63%	86.73%	86.57%	86.40%	86.20%	86.07%	85.89%	85.82%	85.82%	86.4%
Mental Health Carve-Out Drugs	74.51%	74.36%	74.45%	74.17%	74.23%	73.93%	74.05%	73.87%	73.89%	73.82%	73.63%	73.67%	74.0%
FFS Physical Health Drugs	95.75%	95.62%	95.59%	95.53%	95.46%	95.76%	95.62%	95.76%	95.84%	95.67%	95.84%	95.80%	95.7%
Encounter Physical Health Drugs	89.04%	88.95%	88.79%	88.62%	88.75%	88.58%	88.44%	88.20%	88.02%	87.83%	87.78%	87.78%	88.4%

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

Last Updated: July 18, 2019

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

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	LATUDA	Antipsychotics, 2nd Gen	$5,885,689	15.8%	4,917	$1,197	Y
2	INVEGA SUSTENNA	Antipsychotics, Parenteral	$2,807,587	7.5%	1,428	$1,966	Y
3	ABILIFY MAINTENA	Antipsychotics, Parenteral	$1,400,412	3.8%	718	$1,950	Y
4	REXULTI	Antipsychotics, 2nd Gen	$1,371,832	3.7%	1,246	$1,101	V
5	VRAYLAR	Antipsychotics, 2nd Gen	$1,023,776	2.8%	915	$1,119	Y
6	INVEGA TRINZA	Antipsychotics, Parenteral	$683,346	1.8%	118	$5,791	Y
7	FLUOXETINE HCL	Antidepressants	$543,003	1.5%	33,600	$16	Y
8	SAPHRIS	Antipsychotics, 2nd Gen	$532,744	1.4%	844	$631	Y
9	TRINTELLIX	Antidepressants	$515,571	1.4%	1,339	$385	V
10	PALIPERIDONE ER	Antipsychotics, 2nd Gen	$509,473	1.4%	1,822	$280	V
11	BUPROPION XL	Antidepressants	$485,861	1.3%	24,950	$19	V
12	SERTRALINE HCL	Antidepressants	$446,854	1.2%	44,440	$10	Y
13	DULOXETINE HCL	Antidepressants	$433,629	1.2%	30,746	$14	V
14	VIIBRYD	Antidepressants	$409,681	1.1%	1,470	$279	V
15	TRAZODONE HCL	Antidepressants	$396,382	1.1%	38,869	$10	
16	ATOMOXETINE HCL*	ADHD Drugs	$386,342	1.0%	5,636	$69	Y
17	ARISTADA	Antipsychotics, Parenteral	$368,636	1.0%	178	$2,071	Y
18	RISPERDAL CONSTA*	Antipsychotics, Parenteral	$352,039	0.9%	402	$876	Y
19	ENBREL SURECLICK*	Biologics for Autoimmune Conditions	$300,141	0.8%	80	$3,752	Y
20	VENLAFAXINE HCL ER	Antidepressants	$299,962	0.8%	1,782	$168	V
21	LAMOTRIGINE ER	Antiepileptics (oral & rectal)	$295,471	0.8%	2,057	$144	V
22	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	$275,188	0.7%	17,739	$16	
23	Epoetin Alfa, 100 Units Esrd	Physican Administered Drug	$265,199	0.7%	1,433	$185	
24	ESCITALOPRAM OXALATE	Antidepressants	$257,335	0.7%	26,008	$10	Y
25	ARIPIPRAZOLE	Antipsychotics, 2nd Gen	$235,911	0.6%	14,596	$16	V
26	LAMOTRIGINE	Antiepileptics (oral & rectal)	$234,776	0.6%	23,143	$10	Y
27	CONCERTA*	ADHD Drugs	$232,870	0.6%	915	$255	N
28	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$222,855	0.6%	20	$11,143	Y
29	AMITRIPTYLINE HCL	Antidepressants	$220,637	0.6%	14,723	$15	Y
30	EPCLUSA*	Hepatitis C, Direct-Acting Antivirals	$201,794	0.5%	9	$22,422	Y
31	Inj., Emicizumab-Kxwh 0.5 Mg	Physican Administered Drug	$195,828	0.5%	10	$19,583	
32	CITALOPRAM HBR	Antidepressants	$192,450	0.5%	21,713	$9	Y
33	VENLAFAXINE HCL ER	Antidepressants	$190,047	0.5%	15,153	$13	Y
34	QUETIAPINE FUMARATE*	Antipsychotics, 2nd Gen	$181,274	0.5%	15,718	$12	Y
35	BIKTARVY	HIV	$173,771	0.5%	66	$2,633	Y
36	Inj Pembrolizumab	Physican Administered Drug	$170,166	0.5%	65	$2,618	
37	LANTUS SOLOSTAR*	Diabetes, Insulins	$168,164	0.5%	515	$327	Y
38	Inj, Nusinersen, 0.1mg	Physican Administered Drug	$167,178	0.4%	2	$83,589	
39	FETZIMA	Antidepressants	$161,808	0.4%	401	$404	V
40	Inj., Rituximab, 10 Mg	Physican Administered Drug	$157,323	0.4%	66	$2,384	
		Top 40 Aggregate:	**$23,353,004**		**349,852**	**$4,187**	
		All FFS Drugs Totals:	**$37,197,291**		**662,301**	**$544**	

*** Drug requires Prior Authorization**

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

Last updated: July 18, 2019

Drug Use Research & Management Program
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Top 40 Physical Health Drugs by Gross Amount Paid (FFS Only) - Second Quarter 2019

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	ENBREL SURECLICK*	Biologics for Autoimmune Conditions	$300,141	2.4%	80	$3,752	Y
2	Epoetin Alfa, 100 Units Esrd	Physican Administered Drug	$265,199	2.1%	1,433	$185	
3	CONCERTA*	ADHD Drugs	$232,870	1.9%	915	$255	N
4	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$222,855	1.8%	20	$11,143	Y
5	EPCLUSA*	Hepatitis C, Direct-Acting Antivirals	$201,794	1.6%	9	$22,422	Y
6	Inj., Emicizumab-Kxwh 0.5 Mg	Physican Administered Drug	$195,828	1.6%	10	$19,583	
7	BIKTARVY	HIV	$173,771	1.4%	66	$2,633	Y
8	Inj Pembrolizumab	Physican Administered Drug	$170,166	1.4%	65	$2,618	
9	LANTUS SOLOSTAR*	Diabetes, Insulins	$168,164	1.4%	515	$327	Y
10	Inj, Nusinersen, 0.1mg	Physican Administered Drug	$167,178	1.4%	2	$83,589	
11	Inj., Rituximab, 10 Mg	Physican Administered Drug	$157,323	1.3%	66	$2,384	
12	HUMIRA PEN*	Biologics for Autoimmune Conditions	$136,291	1.1%	60	$2,272	Y
13	Etonogestrel Implant System	Physican Administered Drug	$129,118	1.0%	225	$574	
14	NOVOLOG FLEXPEN	Diabetes, Insulins	$124,046	1.0%	272	$456	Y
15	VYVANSE*	ADHD Drugs	$110,389	0.9%	777	$142	Y
16	ENBREL*	Biologics for Autoimmune Conditions	$109,808	0.9%	16	$6,863	Y
17	HUMIRA*	Biologics for Autoimmune Conditions	$106,654	0.9%	22	$4,848	Y
18	ALBUTEROL SULFATE HFA	Beta-Agonists, Inhaled Short-Acting	$105,689	0.9%	2,506	$42	Y
19	LANTUS	Diabetes, Insulins	$102,996	0.8%	296	$348	Y
20	Factor Viii Pegylated Recomb	Physican Administered Drug	$102,242	0.8%	5	$20,448	
21	MAKENA*	Progestational Agents	$99,633	0.8%	50	$1,993	Y
22	NUVARING	STC 63 - Oral Contraceptives	$99,153	0.8%	377	$263	
23	Factor Viii Recombinant Nos	Physican Administered Drug	$95,791	0.8%	5	$19,158	
24	Mirena, 52 Mg	Physican Administered Drug	$95,780	0.8%	150	$639	
25	BUPRENORPHINE-NALOXONE*	Substance Use Disorders, Opioid & Alcohol	$94,522	0.8%	1,287	$73	Y
26	HYDROXYPROGESTERONE CAPROAT	Progestational Agents	$93,736	0.8%	38	$2,467	N
27	Infliximab Not Biosimil 10mg	Physican Administered Drug	$93,279	0.8%	82	$1,138	
28	FLOVENT HFA	Corticosteroids, Inhaled	$92,643	0.7%	585	$158	Y
29	VIMPAT	Antiepileptics (oral & rectal)	$88,275	0.7%	200	$441	Y
30	ADVATE	Antihemophilia Factors	$88,102	0.7%	5	$17,620	
31	TRUVADA	HIV	$86,341	0.7%	76	$1,136	Y
32	STELARA*	Biologics for Autoimmune Conditions	$84,933	0.7%	6	$14,156	N
33	ORKAMBI*	Cystic Fibrosis	$84,053	0.7%	12	$7,004	N
34	OTEZLA*	Biologics for Autoimmune Conditions	$83,580	0.7%	28	$2,985	N
35	Injection, Nivolumab	Physican Administered Drug	$81,777	0.7%	36	$2,272	
36	GENVOYA	HIV	$80,410	0.7%	29	$2,773	Y
37	Aflibercept Injection	Physican Administered Drug	$76,892	0.6%	172	$447	
38	SPIRIVA	Anticholinergics, Inhaled	$76,525	0.6%	201	$381	Y
39	HUMALOG	Diabetes, Insulins	$75,662	0.6%	237	$319	Y
40	CHOLBAM*	Bile Therapy	$74,710	0.6%	1	$74,710	
		Top 40 Aggregate:	**$5,028,321**		**10,937**	**$8,375**	
		All FFS Drugs Totals:	**$12,361,157**		**185,225**	**$560**	

*** Drug requires Prior Authorization**

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

Last updated: July 18, 2019

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Drug Class Literature Scan: Beta Agonists, Inhaled Short-Acting

Date of Review: July 2019

Date of Last Review: September 2015
Literature Search: September/01/2015 – 06/06/2019

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

Purpose of Review:
The purpose of this literature scan is to provide new comparative effectiveness and safety evidence for short-acting beta agonists (SABA) medications published since the last literature scan.

Conclusions:
- New evidence to provide guidance for the preferred drug list (PDL) was synthesized from two new guidelines from the National Institute for Health and Care Excellence (NICE), and two systematic reviews from Cochrane Systematic Reviews.[1-4]
- The identified literature supports current policy and prior authorization criteria for short-acting beta agonist (SABA) medications in the treatment of asthma, chronic obstructive pulmonary disease (COPD), adults with cough or bronchitis as well as bronchiolitis in infants and children.

Hospitalizations
- Patients presenting to the emergency department (ED) who received combination SABA and inhaled anticholinergic therapy were less likely to be hospitalized (risk ratio [RR] 0.72, 95% confidence interval [CI] 0.59 to 0.87; participants = 2120; studies = 16; I^2 = 12%; moderate quality of evidence).[1] An estimated 65 fewer patients per 1000 would require hospitalization after receiving combination therapy (95% 30 to 95), compared to 231 per 1000 patients receiving SABA alone.[1] Although combination inhaled therapy was more effective than SABA treatment alone in reducing hospitalization in participants with severe asthma exacerbations, this was not found for participants with mild or moderate exacerbations (test for difference between subgroups P = 0.02).[1]

Recommendations:
- Recommend no changes to the current PDL for inhaled short-acting beta agonist medications (SABAs) based upon clinical efficacy.
- Evaluate comparative drug costs in executive session.

Summary of Prior Reviews and Current Policy

- As of September 2015, SABAs were delineated into their own PDL class, separate from maintenance inhaler therapies for the treatment of asthma and COPD.
- In adults and children with asthma and adults with COPD there remained insufficient evidence to determine relative differences in efficacy or effectiveness between albuterol and levalbuterol and between the different inhalation formulations.
- There was insufficient evidence to determine a relative difference in efficacy, effectiveness, safety or adverse events in subgroups of patients' base demographics, comorbidities or pregnancy with short-acting, inhaled beta-agonist medications (SABAs).
- Albuterol solution, nebulized solution and HFA are preferred products on the PDL. There is 100% utilization of preferred therapies.

Methods:

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

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

New Systematic Reviews:

Cochrane - Combined inhaled Beta-agonist and Anticholinergic Agents for Emergency Management in Adults with Asthma

Inhaled short-acting anticholinergics (SAAC) and SABA are effective therapies for adult patients with acute asthma who present to the ED.[1] A systematic search and meta-analysis was conducted regarding the effectiveness of combined inhaled therapy (SAAC + SABA agents) vs. SABA alone to reduce hospitalizations in adult patients presenting to the ED with an exacerbation of asthma. Randomized or controlled clinical trials comparing the effectiveness of combined inhaled therapy (SAAC and SABA) to SABA treatment alone to prevent hospitalizations in adults (16 y/o or older) with acute asthma in the emergency department were considered for inclusion. Studies which included less than 20% of the total patient population as having comorbid COPD and having data where by patients without comorbid COPD could be extracted were also included for analysis.[1] Included were 23 studies of high-risk or unclear bias that involved a total of 2724 enrolled patients. The primary outcome measure was inclusive of the proportion of patients requiring hospitalization. Secondary outcomes were also inclusive of ED length of stay, number of bronchodilator treatments required, adverse events, symptom scores, quality of life and continuous data from pulmonary function testing.

Overall, patients receiving combination inhaled therapy were less likely to be hospitalized (RR 0.72, 95% CI 0.59 to 0.87; N = 2120; studies = 16; I^2 = 12%; moderate quality of evidence).[1] An estimated 65 fewer patients per 1000 would require hospitalization after receiving combination therapy (95% 30 to 95), compared to 231 per 1000 patients receiving SABA alone.[1] Although combination inhaled therapy was more effective than SABA treatment alone in reducing hospitalization in patients with severe asthma exacerbations, but not for participants with mild or moderate exacerbations (test for difference between subgroups P = 0.02).[1]
Patients receiving combination therapy were more likely to experience improved forced expiratory volume in one second (FEV_1) (MD 0.25 L, 95% CI 0.02 to 0.48; participants = 687; studies = 6; I^2 = 70%; low quality of evidence), peak expiratory flow (PEF) (MD 36.58 L/min, 95% CI 23.07 to 50.09; participants = 1056; studies

= 12; I^2 = 25%; very low quality of evidence), increased percent change in PEF from baseline (MD 24.88, 95% CI 14.83 to 34.93; participants = 551; studies = 7; I^2 = 23%; moderate quality of evidence), and were less likely to return to the ED for additional care (RR 0.80, 95% CI 0.66 to 0.98; participants = 1180; studies = 5; I^2 = 0%; moderate quality of evidence) than participants receiving SABA alone.[1] Participants receiving combination inhaled therapy were more likely to experience adverse events than those treated with SABA agents alone (OR 2.03, 95% CI 1.28 to 3.20; participants = 1392; studies = 11; I^2 = 14%; moderate quality of evidence).[1] Patients receiving combination therapy, 103 per 1000 were likely to report adverse events (95% 31 to 195 more) compared to 131 per 1000 patients receiving SABA alone.[1]

Cochrane: Beta-2-agonists for acute cough or a clinical diagnosis of acute bronchitis

A systematic review and sensitivity analysis was conducted in determining whether beta-2 agonists (oral and inhaled albuterol, and inhaled fenoterol [not available in the US]) improve acute bronchitis symptoms in people with no underlying pulmonary disease such as asthma, COPD or pulmonary fibrosis.[2] Primary study outcomes were daily cough scores, the number of patients still coughing at the end of the trial and adverse effects from the medication regimen being evaluated. Secondary outcomes were inclusive of but not limited to presentation characteristics of the cough, limitations in daily activities of living and general well-being. Randomized controlled trials (RCTs) which allocated patients (adults, or children over two years of age) with acute bronchitis or acute cough and without known pulmonary disease to beta-2-agonist versus placebo, no treatment or alternative treatment were considered for inclusion.[2] Excluded were studies which contained patients who had pre-existing pulmonary disease, cystic fibrosis and another acute respiratory illness such as sinusitis, pertussis or pneumonia. Eligible trials in children and adult population were analyzed separately.

Two trials of moderate quality in children (n = 134) with no evidence of airflow restriction did not find any benefits from oral beta-2- agonists.[2] Five trials in adults (n = 418) had mixed results but overall summary statistics did not reveal any significant benefits from oral (3 trials) nor from inhaled (3 trials) beta-2-agonists. Three studies with low-quality evidence demonstrated no significant differences in daily cough scores, nor in the percentage of adults still coughing after seven days (control group 71%; RR 0.86, 95% CI 0.63 to 1.18; 220 participants).[2] In one trial, subgroups with evidence of airflow limitation had lower symptom scores if given beta-2-agonists. However investigators noted quicker resolution of cough with beta-2-agonists were those with a higher proportion of people wheezing at baseline.

Authors concluded that at the time of this systematic review there was no evidence to support the use of beta-2-agonists in children (over 2 years of age) or adults with acute cough who do not have evidence of airflow restriction. Beta-2-agonists may reduce symptoms, including cough, in people with evidence of airflow restriction. However, this potential benefit is not well supported by the available data and must be weighed against the adverse effects associated with their use.

After review, twenty-four 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:

NICE- Diagnosis & Management of Bronchiolitis in Children

NICE developed and published guidance regarding diagnosis and management of bronchiolitis in children in 2015.[3] Bronchiolitis is the most common lower respiratory tract infection in the first year of life: one in five infants is affected and 2-3% are hospitalized. Mild cases of bronchiolitis can be managed at home, but infants with severe respiratory distress, difficulty taking adequate oral fluids, or with apnea require secondary care. Inhaled and nebulized SABAs, corticosteroids (ICS) and anticholinergic medications are not recommended in the management of bronchiolitis in infants. NICE guidelines regarding infant

bronchiolitis management also advise against the usage of any of the following medication s (nebulized, inhaled and/or oral): antibiotics, hypertonic saline, adrenaline, salbutamol, montelukast and/or systemic corticosteroids.[3]

NICE – Asthma Diagnosis, Monitoring and Chronic Asthma Management

A 2017 NICE guidance updated the management of chronic asthma in children, young people and adults.[4] The pharmacological recommendations for maintenance therapy were reviewed in a previous update; therefore, SABA use will be presented and discussed in this review. New guidance recommendations mirror previous statements of using SABA first line (**Table 1**).

Table 1. NICE Recommendations for the Use of SABA Therapy in Chronic Asthma[4]

Pharmacotherapy for Adults (17 years and older) with Newly Diagnosed or Uncontrolled Asthma
▪ Offer a SABA for reliever therapy: SABA monotherapy can be considered for adults who have infrequent, short-lived wheeze and normal lung function
▪ SABA can be used as reliever therapy in patients who continue to have uncontrolled asthma on a MART* regimen and are switching to a fixed-dose ICS and LABA
Pharmacotherapy for children and young people (5 to 16 years) with newly diagnosed or uncontrolled asthma
▪ 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
▪ 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
▪ SABA as reliever therapy should be used in combination with ICS and LABA in patients who continue to have uncontrolled asthma symptoms on a MART regimen*
Pharmacotherapy for Children Under 5 (5 to 16 year olds) with Suspected or Confirmed Asthma
▪ A SABA should be offered to children with suspected asthma for symptom relief and alongside maintenance therapy.
* 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. Abbreviations: ICS – inhaled corticosteroid; LABA – long-acting beta-agonist; LTRA – leukotriene receptor antagonist; MART – maintenance and reliever therapy; SABA – short-acting beta-agonist

Summary of Additional Guidelines & Clinical Trials for Clinical Context:

Global Initiative for Chronic Obstructive Lung Disease (GOLD) - 2019

The GOLD guidelines are produced on an annual basis to provide strategies for diagnosis, management and prevention of COPD.[5] GOLD 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.[5] Therefore, guideline recommendations for pharmaceutical management will be provided for clinical context but not relied upon for decisions regarding the PDL. Maintenance medications have been previously presented so only evidence related to SABAs will be presented. GOLD recommends the use of SABAs in patients with COPD who present with 0 to 1 moderate exacerbations. Inhaled bronchodilators are recommended over oral bronchodilators, which have demonstrated prevention and reduction in symptoms (Evidence level A [recommendation based on high-quality evidence]).[5] Regular and as needed use of SABA or short-acting muscarinic antagonists

(SAMA) have shown to reduce symptoms and improve FEV1 and are recommended based on level A evidence. Combination of SABA and SAMA are superior in reducing symptoms and improving FEV1 compared to either entity alone (Evidence level A).[5]

New Formulations:

- ProAir Digihaler – A dry powder inhaler that meters 117 mcg of albuterol (equivalent to 97 mcg of albuterol base) from the device reservoir and delivers 108 mcg of albuterol (equivalent to 90 mcg of albuterol base) from the mouthpiece per actuation was approved in 2019.[6] ProAir ® Digihaler™ is indicated for the treatment or prevention of bronchospasm in patients aged four years and older with reversible obstructive airway disease, and for prevention of exercise-induced bronchospasm (EIB) in patients aged four years and older. ProAir Digihaler contains a built-in electronic module which detects, records, and stores data on inhaler events for transmission to the mobile ProAir ® Digihaler™ contains built-in sensors that detect when the inhaler is used and measure inspiratory flow. Use of the App is not required for administration of medication to the patient.[6]
- Albuterol – A generic version of ProAir hydrofluoroalkane (HFA) albuterol metered dose inhaler, manufactured by Teva, was approved in 2019.[7]
- Albuterol – An authorized generic version of Ventolin metered dose inhaler, manufactured by GSK, was approved in 2019.[8]

New FDA Safety Alerts:

No new safety alerts identified.

References:

1. Kirkland SW, Vandenberghe C, Voaklander B, et al. Combined inhaled beta-agonist and anticholinergic agents for emergency management in adults with asthma. *Cochrane Database Syst Rev*. 2017;1:CD001284.
2. Becker LA, Hom J, Villasis-Keever M, et al. Beta 2-agonists for acute cough or a clinical diagnosis of acute bronchitis. *Cochrane Database Syst Rev*. 2015(9):CD001726.
3. National Institute for Health and Care Excellence. Bronchiolitis in children: diagnosis and management. *NICE Guideline* [NG9] Published date: June 2015 https://www.nice.org.uk/guidance/ng9. Accessed April 23, 2019.
4. National Institute for Health and Care Excellence. Asthma: diagnosis, monitoring and chronic asthma management. NICE Guideline. November 2017. Available at: nice.org.uk/guidance/ng80. Accessed April 23, 2019.
5. GOLD 2019 Global Strategy for the Diagnosis, Management and Prevention of COPD. Glob Initiat Chronic Obstr Lung Dis - GOLD. http://goldcopd.org/gold-2018-global-strategy-diagnosis-management-prevention-copd/. Published November 2018. Accessed April 23, 2019.17.
6. ProAir Digihaler Prescribing Information. Teva Respiratory LLC, Frazer PA. December 2018
7. Albuterol HFA. Prescribing Information. Teva Respiratory LLC, Frazer, PA. March 2019.
8. Albuterol HFA. Prescribing Information. Prasco GlaxoSmithKline, LLC, Research Triangle Park, NC. March 2019.

Appendix 1: Current Preferred Drug List

Short-Acting Beta-Agonists

Generic	Brand	Form	PDL
albuterol sulfate	ALBUTEROL SULFATE HFA	HFA AER AD	Y
albuterol sulfate	PROAIR HFA	HFA AER AD	Y
albuterol sulfate	PROVENTIL HFA	HFA AER AD	Y
albuterol sulfate	VENTOLIN HFA	HFA AER AD	Y
albuterol sulfate	ALBUTEROL SULFATE	SOLUTION	Y
albuterol sulfate	AIRET	VIAL-NEB	Y
albuterol sulfate	ALBUTEROL SULFATE	VIAL-NEB	Y
albuterol sulfate	PROAIR RESPICLICK	AER POW BA	N
albuterol	ALBUTEROL	AER REFILL	N
levalbuterol HCl	LEVALBUTEROL CONCENTRATE	VIAL-NEB	N
levalbuterol HCl	LEVALBUTEROL HCL	VIAL-NEB	N
levalbuterol HCl	XOPENEX	VIAL-NEB	N
levalbuterol HCl	XOPENEX CONCENTRATE	VIAL-NEB	N
levalbuterol tartrate	LEVALBUTEROL TARTRATE HFA	HFA AER AD	N
levalbuterol tartrate	XOPENEX HFA	HFA AER AD	N

Appendix 2: New Comparative Clinical Trials

A total of 29 citations were manually reviewed from the initial literature search. After further review, 25 were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical).

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R)** 1946 to May Week 5 2019

Search Strategy:

#	Searches	Results
1	Albuterol/ or albuterol.mp.	10220
2	levalbuterol.mp. or Levalbuterol/	133
3	1 or 2	10231
4	limit 3 to (english language and humans and yr="2015 -Current")	577
5	limit 4 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	29

Appendix 5: Key Inclusion Criteria

Population	Patients with asthma, chronic obstructive pulmonary disease and other lung diseases treated with SABAs
Intervention	SABA listed in Appendix 1
Comparator	Active comparisons of drugs listed in Appendix 1
Outcomes	Symptom Improvement Morbidity Mortality Serious Adverse Events Discontinuation from Serious Adverse Events
Timing	Any study duration; literature search from 9/1/2015 to 6/6/2019
Setting	Outpatient

ProDUR Report for April through June 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	12	2	0	10	0.01%	16.7%
DC (Drug/Inferred Disease Interaction)	Quetiapine billed and condition on file for Congenital Long QT Sundrome	Set alert/Pay claim	1,441	340	0	1,099	1.27%	23.6%
DD (Drug/Drug Interaction)	Linezolid being billed and patient is on an SNRI	Set alert/Pay claim	135	30	0	105	0.10%	22.2%
ER (Early Refill)	Previously filled 30 day supply and trying to refill after 20 days (80% = 24 days)	Set alert/Deny claim	75,666	13,768	127	61,759	68.50%	18.2%
ID (Ingredient Duplication)	Oxycodone IR 15mg billed and patient had Oxycodone 40mg ER filled in past month	Set alert/Pay claim	23,126	5,828	15	17,235	20.90%	25.2%
LD (Low Dose)	Divalproex 500mg ER billed for 250mg daily (#15 tabs for 30 day supply)	Set alert/Pay claim	863	159	0	701	0.73%	18.4%
MC (Drug/Disease Interaction)	Bupropion being billed and patient has a seizure disorder	Set alert/Pay claim	822	213	1	608	0.70%	25.9%
MX (Maximum Duration of Therapy)		Set alert/Pay claim	640	182	0	452	0.53%	28.4%
PG (Pregnancy/Drug Interaction)	Accutane billed and client has recent diagnosis history of pregnancy	Set alert/Deny claim	23	19	0	4	0.02%	82.6%
TD (Therapeutic Duplication)	Diazepam being billed and patient recently filled an Alprazolam claim.	Set alert/Pay claim	7,691	2,063	1	5,614	6.90%	26.8%
		Totals	**110,419**	**22,604**	**144**	**87,587**	**99.67%**	**20.5%**

ProDUR Report for April through June 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)	1,303	146	1,157	11,253	11.6%	11.2%
ER	Lorazepam	454	135	319	13,248	3.4%	29.7%
ER	Alprazolam	299	46	253	8,830	3.4%	15.4%
ER	Diazepam	162	46	116	4,848	3.3%	28.4%
ER	Buspirone (Buspar)	2,053	348	1,705	26,928	7.6%	17.0%
ER	Lamictal (Lamotrigine)	4,330	821	3,509	35,823	12.1%	19.0%
ER	Seroquel (Quetiapine)	3,523	667	2,853	25,583	13.8%	18.9%
ER	Risperdal (Risperidone)	1,801	370	1,430	13,498	13.3%	20.5%
ER	Abilify (Aripiprazole)	2,645	421	2,224	21,500	12.3%	15.9%
ER	Wellbutrin (Bupropion)	4,574	778	3,796	53,938	8.5%	17.0%
ER	Hydrocodone/APAP	24	10	14	2,630	0.9%	**41.7%**
ER	Oxycodone	71	25	46	1,877	3.8%	**35.2%**
ER	Oxycodone/APAP	18	7	11	888	2.0%	**38.9%**
ER	Tramadol	16	3	13	769	2.1%	18.8%
ER	Zoloft (Sertraline)	5,562	984	4,577	55,407	10.0%	17.7%
ER	Prozac (Fluoxetine)	4,023	619	3,403	43,312	9.3%	15.4%
ER	Lexapro (Escitalopram)	3,020	472	2,548	33,339	9.1%	15.6%
ER	Celexa (Citalopram)	2,209	268	1,941	26,153	8.4%	12.1%
ER	Trazodone	5,082	795	4,287	48,505	10.5%	15.6%

ProDUR Report for April through June 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	April	3,320	135	233	1,007	5	1,789	0	151
ER	May	3,736	173	321	1,000	6	2,075	0	161
ER	June	2,803	176	216	767	4	1,525	0	115
	Total =	**9,859**	**484**	**770**	**2,774**	**15**	**5,389**	**0**	**427**
	Percentage of total overrides =		**4.9%**	**7.8%**	**28.1%**	**0.2%**	**54.7%**	**0.0%**	**4.3%**

SUPPORT ACT and ProDUR:

CMS has issued new Federal legislation for States to prospectively monitor opioids and CNS depressants, specifically benzodiazepines and antipsychotics based on requirements of the Substance Use Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act (SUPPORT Act).
More specifically, Section 1004, section (2) Drug Utilization Review Requirements (oo)(1)(A)(i)(III):
‘‘ a claims review automated process (as designed and implemented by the State) that monitors when an individual enrolled under the State plan (or under a waiver of the State plan) is concurrently prescribed opioids and—‘‘(aa) benzodiazepines; or ‘‘(bb) antipsychotics”. In response to the FDA Drug Safety Communication requiring strong warnings for opioids and CNS Depressants when used in combination, FDB developed Severity level III DDIM monographs for these interactions. These need to be incorporated into the MMIS ProDUR alert program along with the ability to add other monograms as the State may need through a configurable group in Reference.

FDB ProDUR provides the files in 3 sections for Drug-Drug Interactions:
Severity Level 1: SL1s- MAJOR interaction.
Severity Level 2: SL2s- SEVERE Interaction.
Severity Level 3: SL3s- MODERATE Interaction (Currently there are over 1,000 identified drug interactions in this level)

Below we see what each of our accounts currently receive from the National system.
AL SL1
CT SL1,2
DE SL1,2
KS SL1,2
OK SL1,2
OR SL1 (Major only)
PA SL1
RI SL1
WI SL1,2

Severity Level 1, “Contraindicated Drug Combination”
Drug combinations generally should not be dispensed or administered to the same patient. A manufacturer label warning that indicates the contraindication warrants inclusion of a drug combination in this category, regardless of clinical evidence or lack of clinical evidence to support the contraindication.

Severity Level 2, “Severe Interaction”
Interactions that produce serious consequences in most patients. However, monitoring and/or titrating the agent(s) involved in severe interactions can significantly minimize the risk of adverse effects. If a drug product’s label contains the phrase, “concurrent use should be avoided,” the interaction is assigned this severity level. The drug combination may be absolutely contraindicated in some but not all patients, and the corresponding DDIM monograph contains information on how to identify these patients. The DDIM monograph also includes drugs that patients can take on a staggered schedule but should never take at the same time. Actions required for severe interactions include, but are not

limited to, discontinuing one or both agents, adjusting dosage, altering administration scheduling, and providing additional patient monitoring.

Severity Level 3, “Moderate Interaction”
Interactions of moderate severity. The clinician should assess the patient’s characteristics and take action as needed. Actions required for moderate interactions include, but are not limited to, discontinuing one or both agents, adjusting dosage, altering administration scheduling, and providing additional patient monitoring.

Drug-Drug severity level for the below Drug-Drug Interaction Module (DDIM’s) are coded as a 3 in the FDB Data:

2792 29208 Opioids (Extended Release)/Benzodiazepines Moderate
2793 29207 Opioids (Immediate Release)/Benzodiazepines Moderate
2798 29202 Opioids (Extended Release)/Antipsychotics; Phenothiazines Moderate
2799 29201 Opioids (Immediate Release)/Antipsychotics; Phenothiazines Moderate

From FDB:
In response to the FDA Drug Safety Communication of August 31, 2016, requiring strong warnings for opioids and CNS Depressants (such as olanzapine, an antipsychotic) when used in combination (http://www.fda.gov/Drugs/DrugSafety/ucm518473.htm), FDB researched which option, or options, to provide customers that are the most practical and implementable solutions and sought feedback from customers who had submitted inquiries on the subject to Customer Support and from all other customers through Customer Connection and the FDB Community.

On the December 8, 2016 production build, the following monographs were added to DDIM:

DDIM:
DDIM ID Side B ID Full Description Severity
2788 29212 Opioids (Cough and Cold)/Benzodiazepines Severe
2789 29211 Opioids (Cough and Cold)/Sleep Drugs; Tranquilizers Severe
2790 29210 Opioids (Cough and Cold)/Muscle Relaxants Severe
2791 29209 Opioids (Cough and Cold)/Antipsychotics; Phenothiazines Severe
2792 29208 Opioids (Extended Release)/Benzodiazepines Moderate
2793 29207 Opioids (Immediate Release)/Benzodiazepines Moderate
2794 29206 Opioids (Extended Release)/Sleep Drugs; Tranquilizers Moderate
2795 29205 Opioids (Immediate Release)/Sleep Drugs; Tranquilizers Moderate
2796 29204 Opioids (Extended Release)/Muscle Relaxants Moderate
2797 29203 Opioids (Immediate Release)/Muscle Relaxants Moderate
2798 29202 Opioids (Extended Release)/Antipsychotics; Phenothiazines Moderate
2799 29201 Opioids (Immediate Release)/Antipsychotics; Phenothiazines Moderate

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

Retro-DUR Intervention History by Quarter FFY 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	$29,080			
	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	$74,261			

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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	81	9
		Total Faxes Successfully Sent	35	48	30	4
		Prescriptions Changed to Recommended Dose Within 3 Months of Fax Sent	29	29	7	
		Prescriptions Changed to Alternative Dose Within 3 Months of Fax Sent	6	26	6	
		Prescriptions Unchanged after 3 Months of Fax Sent	50	42		
		Safety Monitoring Profiles Identified	3	2		
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Faxes Sent	$55,459	$42,715	$7,391	

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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
Non-Adherence	Antipyschotics for Schizophreniacs	Total patients identified			22	9
		Total prescribers identified			22	9
		Prescribers successfully notified			22	
		Patients with claims for the same antipsychotic within the next 90 days			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
Profile Review	Children under age 12 antipsychotic	RetroDUR_Profiles Reviewed	46	77	87	
	Children under age 18 on 3 or more psychotropics	RetroDUR_Profiles Reviewed	9	5	16	
	Children under age 18 on any psychotropic	RetroDUR_Profiles Reviewed	85	110	120	
	Children under age 6 on any psychotropic	RetroDUR_Profiles Reviewed	5	7	14	
	Dose Consolidation Safety Monitoring	RetroDUR_Profiles Reviewed		10		
	High Risk Patients - Asthma	RetroDUR_Profiles Reviewed			12	
	High Risk Patients - Polypharmacy	RetroDUR_Profiles Reviewed	19	12	12	
		RetroDUR_Letters Sent To Providers	5	2	3	
		Provider Responses	0	0	0	
		Provider Agreed / Found Info Useful	0	0	0	
	Lock-In	RetroDUR_Profiles Reviewed	52	5	31	
		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	168	
		RetroDUR_Letters Sent To Providers	5	4	21	
		Provider Responses	0	0	2	
		Provider Agreed / Found Info Useful	0	0	2	

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March, 2019 Volume 9, Issue 3

Non-statin Low-Density Lipoprotein Cholesterol (LDL-C) Lowering Therapy and Cardiovascular Outcomes

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Hypercholesterolemia, and especially elevated low-density lipoprotein cholesterol (LDL-C), is associated with increased risk of atherosclerotic cardiovascular disease (ASCVD). Prevention of ASCVD events involves optimization of treatment that have proven benefits on reduction in ASCVD events and/or cardiovascular (CV) mortality. Until recently, only statins had strong and consistent evidence demonstrating an ASCVD risk reduction. Therefore, statin therapy remains the cornerstone of treatment after therapeutic lifestyle changes (TLC). However, combination therapy to reduce ASCVD risk beyond statin use may be necessary for high-risk populations. The purpose of this newsletter is to review recent data and discuss the place in therapy of non-statin medications. Key recommendations from the recently updated 2018 American College of Cardiology (ACC)/American Heart Association (AHA) Blood Cholesterol guideline will also be discussed.[1,2]

Management of Hypercholesterolemia

After TLC, the 2018 ACC/AHA Blood Cholesterol guideline recommends moderate- or high-intensity statins to patients in which there is evidence of ASCVD risk reduction (Table 1).[1]

Table 1: Statin Benefit Groups

Statin Benefit Group	Recommended Treatment
Clinical ASCVD	High-intensity statin
Severe Hypercholesterolemia (LDL-C ≥ 190 mg/dl)	High-intensity statin
Diabetes age 40-75 and LDL-C ≥ 70 mg/dl	Moderate-to high-intensity statin (based on ASCVD risk factors)
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

A significant change in the guidelines is the re-implementation of a 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 1 major ASCVD event and multiple high-risk conditions (Table 2).[1] The guideline recommendation is to add ezetimibe to maximally tolerated statin therapy as a first step in lowering LDL-C, followed by a proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor if LDL-C remains ≥ 70 mg/dl on both statin and ezetimibe therapy for very high risk only.[1] Ezetimibe is recommended as first-line add on therapy because it is widely available as a generic and is well tolerated. Additionally, ezetimibe was allowed at baseline along with a statin in both PCSK9 inhibitor outcome trials.[3,4]

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
Symptomatic PAD	Current Smoking	Heart failure
	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

Ezetimibe is an inhibitor of intestinal cholesterol absorption indicated as an adjunct to reduce elevated cholesterol and LDL-C. Ezetimibe 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.[2] In this trial, simvastatin 40mg/ezetimibe 10mg was compared to simvastatin 40mg in patients who had been hospitalized for an acute coronary syndrome within the preceding 10 days (Table 3).[2] The primary endpoint was a composite of CV death, nonfatal myocardial infarction (MI), unstable angina requiring re-hospitalization, coronary revascularization, or nonfatal stroke. 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 (Table 4). Additionally, the median LDL-C was reduced to 53.7 mg/dl in the ezetimibe group, as compared with 69.5 mg/dl in the simvastatin monotherapy group would still be considered at goal in this population. 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 effect on CV outcomes with ezetimibe/simvastatin combination was not particularly robust.[5] Additionally, a moderate-intensity statin was used as the study comparator which is not consistent with current practice recommendations.

Table 3: Characteristics of Cardiovascular Outcome trials for Non-statins[2-4]

	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 at baseline	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

PCSK9 Inhibitors

Evolocumab (Repatha®) and alirocumab (Praluent®) are subcutaneously injected human monoclonal antibodies that reduce LDL-C by inhibiting PCSK9.[6,7] PCSK9 promotes the degradation of the LDL receptor, resulting in an increase in plasma LDL-C. Both agents are effective at lowering LDL-C and can lower LDL-C by an average of 50% 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.[6,7] 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.[6]

FOURIER Trial (evolocumab)

The FOURIER trial is the first published PCSK9 inhibitor trial that evaluated CV clinical outcomes as the primary outcome (Table 3).[3] It is a parallel group, double-blind, large, good quality randomized controlled trial (RCT) (n=27,654) that included adults with history of clinically evident CVD with LDL-C greater than or equal to 70 mg/dl with at least one major risk factor (diabetes, smoker, age ≥65 years, recent acute coronary syndrome [ACS]) or two minor risk factors (coronary revascularization, residual coronary artery disease [CAD], metabolic syndrome, LDL-C ≥130 mg/dl).

Participants were randomized to evolocumab or placebo. Patients in both groups were on moderate- or high-intensity statin therapy, with or without ezetimibe as background therapy. Only around 5% of those in each group were on ezetimibe, and almost 70% were on high intensity statin.[3] The study population had a relatively well-controlled lipid profile with a median LDL-C of 92 mg/dl and triglycerides of 133 mg/dl. The median duration of follow-up was 26 months.[3] The primary outcome was a CV composite outcome including CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization.

The primary CV composite outcome was modestly reduced with evolocumab compared to placebo (9.8% vs. 11.3%; HR 0.85; 95% [confidence interval] CI 0.79 to 0.92; absolute risk reduction [ARR] 1.5%; number needed to treat [NNT] 67) (Table 4).[3] There was no significant reduction in individual outcomes including CV death or overall mortality. There was numerically a higher rate of overall mortality (3.2% vs. 3.1%) and CV death (1.8% vs. 1.7%) in the evolocumab group compared to placebo. The small reduction of 1.5% in the primary composite outcome was largely driven by a difference in non-fatal events (MI, stroke, or coronary revascularization). Although the follow-up duration was shorter than planned due to a higher than expected event rate (26 of 48 months planned), it was still surprising that there was no trend toward a reduction in death from CV disease.

Consistent with previous studies, LDL-C was significantly reduced with evolocumab compared to placebo, with a least-squares mean reduction of 59% compared to placebo (95% CI, 55 to 57).[3] At 48 weeks, LDL-C was reduced to less than or equal to 70 mg/dl in 87% of evolocumab-treated patients compared to 18% in the placebo group (ARR 69%; NNT 2).

Table 4: Summary of Results from Cardiovascular Outcome Trials[2,3,9]

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

Abbreviations: ARR: absolute risk reduction; CV: cardiovascular; NNT: number needed to treat; NS: non-significant

ODYSSEY OUTCOMES Trial (alirocumab)

The ODYSSEY OUTCOMES trial is a double-blind, placebo-controlled RCT comparing alirocumab to placebo in patients who had been hospitalized with ACS one to 12 months before randomization and had an LDL-C of at least 70 mg/dl on a high-intensity statin (n=18,924).[4] The primary outcome was a CV composite outcome including CV death, MI, stroke, or hospitalization for unstable angina.

The majority of patients qualified with a MI (83%) and the median time from ACS to randomization was 2.6 months. Most patients were stable on a high-intensity statin (89%) and median LDL-C was 92 mg/dl. Unlike the FOURIER trial, dose adjustments were made to avoid sustained LDL-C levels below 15 mg/dl.

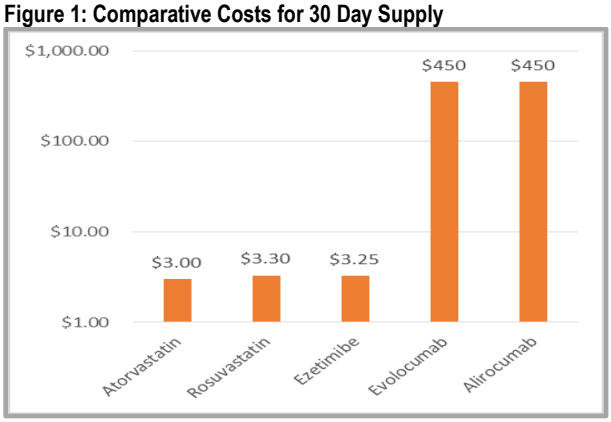
The primary CV composite outcome was reduced with alirocumab compared to placebo (9.5% vs. 11.1%; ARR 1.6%; NNT 63).[4] There was no significant death due to CV causes but unlike the evolocumab trial, there was a significant reduction in overall mortality (Table 4). This difference could be in part due to the longer study duration in the ODYSSEY OUTCOMES.

LDL was significantly reduced from baseline with alirocumab compared to placebo by 62.7% at 4 months.[4] However, the mean LDL-C in the alirocumab increased over the duration of the study from 40 mg/dl at four months to 66 mg/dl at 48 months. This could be due to the blinded dose reduction or crossover to placebo (7.7%) for LDL-C less than 25 mg/dl and 15 mg/dl, respectively.

Safety of PCSK9 inhibitors

There was no difference in serious adverse events or discontinuations due to adverse events in the CV outcome trials with PSCK9 inhibitors. There was also no significant difference in incident of new-onset diabetes between either PCSK9 inhibitor and placebo. Potential risks of adverse neurological effects from sustained, extremely low LDL-C levels have been hypothesized. In a 2-year subgroup analysis of the FOURIER trial designed to detect cognitive changes, no significant difference in cognitive function was observed.[8] However, long-term safety beyond 2-4 years remains unknown and more long-term data is needed.

Figure 1: Comparative Costs for 30 Day Supply



Clinical Use of Non-statin Lipid Lowering Agents

Current standard of care is to optimize TLC and statin therapy for patients with CV disease and for those with a high CV risk. Statins have been shown to reduce all-cause mortality in patients with CV disease (NNT 25), as well as vascular events.[1] Additionally, high intensity statins have shown a greater reduction in events compared to low intensity statins driven by a greater LDL-C lowering ability, highlighting the importance of dose optimization. More recent clinical trials have demonstrated a modest absolute benefit (<2%) on non-fatal CV events with ezetimibe and PCSK9 inhibitors as adjuncts to moderate- to high-intensity statin therapy with no proven CV mortality benefit. The cost versus benefit of PCSK9 inhibitors prevents widespread use (Figure 1), and the ACC/AHA guideline gives them a low-cost value for patients at very high risk of ASCVD.[1] Additionally, the long-term safety of PCSK9 inhibitors remains to be seen.

Non-statin therapy should be reserved for high risk patients with clinical ASCVD who have LDL-C of at least 70 mg/dl on high intensity statin therapy, or those with severe hypercholesterolemia (initial LDL-C ≥ 190 mg/dl), especially familial hypercholesterolemia (FH), with a LDL of at least 100 mg/dl on maximally tolerated statin. Ezetimibe has shown similar benefits as add on therapy over a longer duration (7 years), but at a much lower cost than the PCSK9 inhibitors (Figure 1) and is extremely well tolerated. Ezetimibe is a reasonable first-line add on therapy for patients with CVD with the ability to incrementally lower LDL-C up to 25% on top of statin therapy. There is limited evidence on CV outcomes and a limited place in therapy for other LDL-C lowering agents (fibrates, bile acid sequestrants, niacin, and omega-3 fatty acids), but may still be useful to achieve additional LDL-C lowering in patients with FH.

Oregon Health Plan (OHP) Fee-For-Service (FFS) Policy

- PCSK9 inhibitors are non-preferred and are subject to prior authorization criteria requiring:
  - Clinical ASCVD on high-intensity statin and ezetimibe requiring additional LDL-C lowering
  - Heterozygous or homozygous familial hypercholesterolemia on a maximally tolerated statin

Peer Reviewed By: Bart Duell, M.D., Professor of Medicine, Division of Cardiovascular Medicine School of Medicine at Oregon Health and Science University

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THE OREGON STATE DRUG REVIEW©
AN EVIDENCE BASED DRUG THERAPY RESOURCE http://pharmacy.oregonstate.edu/drug-policy/newsletter
May 2019 Volume 9, Issue 4

Update on Medications Used to Manage Opioid Use Disorder and Opioid Withdrawal

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The widespread use of opioids has resulted in an unprecedented increase in the number of patients who struggle with opioid addiction. Opioid use disorder (OUD) is used to define this condition, which applies to patients with a problematic pattern of opioid use. Effective treatment strategies to assist patients to successfully taper off opioids are widely sought. Methadone, buprenorphine, and naltrexone are Food and Drug Administration (FDA)-approved to manage OUD. The purpose of this newsletter is to provide an update on newer buprenorphine formulations approved by the FDA for treatment of OUD and to review the evidence for lofexidine, a new medication approved to manage opioid withdrawal symptoms for patients who are detoxifying.

Guidance on the Management of Opioid Use Disorder

For patients with a diagnosis of OUD, the Veterans Affairs and Department of Defense (VA/DoD) guideline strongly recommends using methadone in an Opioid Treatment Program (OTP) or buprenorphine/naloxone depending on patient preferences.[1] Also, buprenorphine without naloxone is strongly recommended to be used in patients who are pregnant.[1] Extended-release injectable naltrexone is recommended as an option for patients for whom buprenorphine/naloxone or methadone is contraindicated or unavailable, and who have established opioid abstinence for a sufficient period of time.[1] While shown to have similar efficacy as methadone in clinical trials, buprenorphine/naloxone has several advantages over methadone, including a reduced risk of fatal overdose because of its lower potential for respiratory depression.[2] In May 2018, lofexidine (Lucemyra™) received FDA approval for short-term mitigation of severe opioid withdrawal symptoms in adults to facilitate abrupt opioid discontinuation.[3]

In the Oregon Health Plan (OHP) Fee-For-Service (FFS) program, preferred agents to manage OUD include: buprenorphine/naloxone film and sublingual tablets, naltrexone extended-release injection, and naltrexone tablets.

Long Acting Monotherapy Buprenorphine Products

In 2016, the FDA approved Probuphine®, a monotherapy buprenorphine product administered via subdermal implant for management of OUD.[4] The implant embeds buprenorphine in four matchstick-size rods in a patient's upper arm that release medication over a 6 month period.[4] The buprenorphine implant is designed only for patients who have received buprenorphine/naloxone maintenance therapy for at least 3 months.[4]

Efficacy

The efficacy of the Probuphine® implant is based on evidence from one double-blind, 6-month randomized controlled trial (RCT) that compared the 4 simultaneous 80 mg buprenorphine implants with sublingual buprenorphine in adults who met criteria for opioid dependence.[5] All patients in the trial were clinically stable for at least 6 months on sublingual (SL) buprenorphine at 8 mg per day or less.[5] The primary efficacy end point was the proportion of responders, defined as participants with at least 4 of 6 months without evidence of illicit opioid use (based on urine drug screen and self-report composites) by treatment group.[5] A significant proportion of patients in the implant group responded to therapy compared to the SL group (Number Needed to Treat (NNT) = 12).[5] Therapy beyond 1 year is not feasible with Probuphine®, as a second insertion of the implants cannot be placed into a previously used arm.

In 2017, the FDA approved Sublocade™ a once-monthly buprenorphine extended-release subcutaneous injection for management of OUD.[6] Sublocade™ uses a proprietary delivery system that induces the drug to form a solid deposit under the skin, gradually biodegrading into the active therapeutic agent.[6] The safety and efficacy of Sublocade™ were evaluated in two clinical studies in adults with a diagnosis of moderate-to-severe OUD who began treatment with buprenorphine/naloxone sublingual film for at least 7 days before transitioning to the extended-release subcutaneous injection.[6] Response to buprenorphine therapy compared to placebo was measured by urine drug screening and self-reporting of illicit opioid use during the six-month treatment period. The proportion of patients achieving treatment success (defined as patients with ≥80% opioid-free weeks) was statistically significantly higher in groups treated with buprenorphine 300 mg subcutaneously once a month for 6 doses compared to the placebo group (29.1% vs. 2%; $p<0.05$; NNT = 4).[6]

Safety

Probuphine® is not available in retail pharmacies and must be inserted and removed by the certified prescriber.[4] The implants can only be obtained through a restricted Risk Evaluation and Mitigation Strategy (REMS) program that requires specialized training for physicians on insertion and removal techniques, the risks for accidental overdose, and misuse/abuse of opioids.[4]

Sublocade™ has a boxed warning regarding the risks of intravenous self-administration.[6] If the product were to be administered intravenously rather than subcutaneously, the solid deposit containing the drug could cause occlusion, tissue damage or embolus.[6] Sublocade™ must be prescribed and dispensed as part of a REMS program to ensure that the product is not distributed directly to patients.[6] Sublocade™ is provided to health care providers (HCPs) through a restricted program and must be administered to patients in a health care setting. Pharmacies that dispense Sublocade™ are required to complete an enrollment form attesting that they have procedures in place to ensure that Sublocade™ is dispensed only to HCPs and not directly to patients.[6] The safety and efficacy of extended-release buprenorphine have not been established in children or adolescents less than 17 years of age or adults over the age of 65 years.[6]

To date, no systematic reviews comparing the various buprenorphine formulations have been identified.[7] The data from clinical trials indicates that newer long-acting buprenorphine formulations may be

safe for treatment of OUD, but the trials were relatively short in duration (26 weeks or less) and were not powered to detect rare adverse effects.[7] Larger studies with longer treatment durations are required to better understand the safety profile of these newer buprenorphine formulations.[7]

Lofexidine for Opioid Withdrawal Symptoms

In May 2018, lofexidine (Lucemyra™) received FDA approval for management of severe opioid withdrawal symptoms for up to 14 days of treatment.[3] Lofexidine is an alpha2-adrenergic agonist similar to clonidine which reduces the release of norepinephrine and decreases sympathetic tone and lessens the symptoms of withdrawal.[3] Lofexidine may not completely prevent withdrawal symptoms and is not a treatment for OUD as a single agent, but can be used as part of a broader, long-term treatment plan for managing OUD.[3]

Lofexidine Evidence

The safety and efficacy of lofexidine were assessed in one double-blind RCT conducted at 15 U.S. inpatient sites. Patients meeting criteria for opioid dependence were physically dependent on short-acting opioids (e.g., heroin, hydrocodone, or oxycodone).[8] Subjects were randomized 1:1 to receive lofexidine 2.88 mg/day (n=134) or placebo (n=130) for 5 days, followed by an additional 2 days of treatment with placebo prior to discharge on Day 8.[8]

The co-primary efficacy endpoints were mean Short Opioid Withdrawal Scale (SOWS)-Gossop total score on day 3 of treatment and time to study dropout. The SOWS-Gossop assessment is a 10 item, patient-reported outcome instrument. Each item represents a symptom and is evaluated on a scale ranging from a total score of 0 (no symptoms) to 30 (severe symptoms).[9] Studies indicate that a change score of 2 to 4 points on the SOWS-Gossop scale may represent a clinically meaningful improvement.[10] For this trial, the investigators assumed a minimal clinically significant difference of 5 points.[8] The mean SOWS-Gossop scores on day 3 were 8.67 and 6.32 for placebo and lofexidine, respectively, which demonstrated a statistically significant difference between the 2 arms [least squares mean difference (LSMD) = -2.24, 95% Confidence Interval (CI) -3.88 to -0.6; p=0.009].[11] While there was a statistically significant difference, there was no clinical difference between lofexidine and placebo.

Comparative Evidence for Acute Opioid Withdrawal Symptom Management

A high quality systematic review evaluated evidence on safety and efficacy of alpha2-adrengeric agonists (lofexidine and clonidine) in managing the acute phase of opioid withdrawal.[12] Moderate quality evidence from three studies comparing alpha2-adrenergic agonists and placebo showed completion of withdrawal treatment was significantly more likely with an adrenergic agonist (Risk Ratio (RR) 1.95; 95% confidence interval (CI) 1.34 to 2.84) and severe withdrawal was significantly less likely with an adrenergic agonist (RR 0.32; 95% CI 0.18 to 0.57).[12] Upon comparison of alpha2-adrenergic agonists with a methadone taper, moderate quality evidence suggests there is no significant difference in severity of the withdrawal episode (Standardized Mean Difference [SMD] 0.13; 95% CI -0.24 to 0.49).[12] Moderate quality evidence also shows no significant differences were observed in completion rates of withdrawal treatment (RR 0.91; 95% CI 0.75 to 1.11) for the adrenergic agonist versus methadone comparisons.[12]

Comparative Evidence for Withdrawal Completion Rates

A meta-analysis of 5 moderate quality trials supports a conclusion of no difference between buprenorphine and methadone for withdrawal completion rates.[13] In a meta-analysis of 14 trials, buprenorphine was associated with a lower average withdrawal score (indicating less severe withdrawal) compared to lofexidine or clonidine during the treatment episode.[13] Patients receiving buprenorphine were more likely to complete withdrawal treatment compared to adrenergic agonists.[13] Specific results from these trials are summarized in **Table 1**.

Table 1. Comparative Evidence for Buprenorphine in OUD[13]

Comparison	Outcome	Results
Buprenorphine vs. Methadone	Withdrawal Completion Rates	RR 1.04 95% CI 0.91 to 1.20
Buprenorphine vs. Adrenergic Agonists	Average Withdrawal Score	SMD -0.43 95% CI -0.58 to -0.28 Favors buprenorphine
Buprenorphine vs. Adrenergic Agonists	Withdrawal Completion Rates	RR 1.59 95% CI 1.23 to 2.06 Favors buprenorphine

Abbreviations: CI = confidence interval; RR = risk ratio; SMD = standardized mean difference

Table 2. Comparative Costs of OUD Therapies (Acute Phase and Maintenance Phase)

Product	Cost per 30 days*
Buprenorphine 8 mg Sublingual Tablets	$140-$420
Buprenorphine/Naloxone 8/2mg Sublingual Tablets	$250-$750
Suboxone® (Buprenorphine/Naloxone) Film 8/2mg	$245-$735
Probuphine® (Buprenorphine) 80 mg Implants: 6 months	$4950**
Sublocade™ (Buprenorphine) Injection 300-100mg	$1580-$3160
Clonidine 0.1 mg Tablets	$3-$6
Lucemyra™(Lofexidine) 0.18 mg Tablets: 7-14 days	$1740-$4635**
Naltrexone 50 mg Tablets	$85
Vivitrol® (Naltrexone) 380 mg Injection	$1309

*Costs based on Wholesale Acquisition Cost (WAC) and vary based on prescribed dosing regimen.
**Cost is for duration of therapy.

In summary, buprenorphine for the treatment of OUD is available in several formulations: tablet, sublingual film, long-acting injection and implant. Buprenorphine sublingual tablets are restricted for use in pregnant females and all buprenorphine monotherapy products require prior authorization (PA) for the OHP FFS PDL. Lofexidine also requires prior authorization to insure medically appropriate use in FDA-approved indications. Relative costs for the various medications used to manage OUD are outlined in **Table 2.**

Peer Reviewed by: Roger Chou, M.D., Professor of Medicine, Oregon Health and Science University and Dara Johnson, PharmD, BCPP, BCACP, Clinical Pharmacy Specialist, Providence Medical Group.

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RetroDUR Proposal: Concurrent Use of Opioids and CNS depressants

Research Questions:

1. What is the evidence regarding safety issues associated with concurrent utilization of CNS depressants (i.e., benzodiazepines, muscle relaxants, sleep agents, antipsychotics) and opioid medications?
2. How frequently are CNS depressants prescribed in combination with chronic opioid therapy in the Medicaid Fee-For-Service (FFS) population? How frequently are CNS depressants prescribed in combination with chronic opioid therapy in the Medicaid Coordinated Care Organization (CCO) population?
3. What is the average duration of opioid therapy in these patients?
4. Which prescriber types and specialties are associated with concomitant prescribing of antipsychotics and opioids?
5. Are there any patient populations or subgroups who appear to be at higher risk of sedative overdose?

Conclusions:

1. Based on the trends of increased concomitant use of opioid analgesics and benzodiazepines as well as increased harms associated with concomitant use described in several studies, the Food and Drug Administration (FDA) required a new boxed warning about the serious risks of concomitant therapy to be added to the labeling of opioid analgesics, opioid cough medications and benzodiazepines in 2016.[1] One study analyzed the involvement of other CNS depressants (including barbiturates, antipsychotic and neuroleptic drugs, antiepileptic and antiparkinsonian drugs, anesthetics, autonomic nervous system drugs, and muscle relaxants) and found that these CNS depressants were contributory to death in many cases where opioid analgesics were also implicated.[2] Based on this evidence, the FDA recommended the boxed warning for opioid analgesics and opioid cough medications also highlight the risk of concomitant use with other CNS depressants.[1]
2. Prescribing frequency of combination therapy with a CNS depressant and opioid
    a. Over the course of a year, over 48,000 patients were prescribed an opioid and another sedating medication with less than 4 months between prescriptions. Only a small proportion of patients (approximately 12%) had claims for overlapping opioid and sedative therapy for more than 6 weeks.
    b. The majority of patients (n=44,467) were enrolled in a CCO at the time they received their opioid prescription. However, because mental health medications like antipsychotics and benzodiazepines are carved-out and paid for by FFS, a significant number of patients enrolled in a CCO have claims for sedative therapy paid for by FFS. Twenty-five percent of CCO patients had a paid FFS claim for sedative therapy in the 30 days before the opioid and 25% had a subsequent FFS sedative claim in the 30 days after the member was prescribed an opioid.
3. Average duration of opioid therapy
    a. The majority of patients (61-65%) prescribed opioid therapy had a proportion of days covered (PDC) of less than 16% (less than about 30 days) in the 6 months after the opioid index event. About 16% of patients with claims for sedating medication had a PDC for opioids of more than 67% (or approximately 120 days).
4. Prescriber types for concomitant opioid and sedative therapy

a. General practitioners (including physicians, advanced practice nurses, and physician assistants) account for the majority of prescribing in patients with combination therapy with an opioid and another sedating medication. In many cases multiple prescribers are involved in prescribing opioids and sedating medications. Only 43% of patients prescribed overlapping treatment for 6-12 weeks and 35% of patients prescribed combination treatment for more than 12 weeks received both the opioid and sedative from a single provider.

5. Patient populations or subgroups at higher risk of sedative overdose
    a. The overall incidence of hospitalization or emergency department visits due to sedative poisoning or sedative adverse events was small and occurred in only 0.6% of all patients prescribed opioids and sedatives.
    b. Patients prescribed sedatives and opioids from 3 or more prescribers and patients with a prior history of sedative overdose had a slightly higher incidence compared to the total population (2.5% and 5.5%, respectively).

Recommendations:

- Send an educational prescriber letter (**Appendix 1**) notifying them of combination opioid and sedative therapy in the following circumstances (see **Appendix 2** for specific inclusion criteria):
    - Patients with 3 or more unique prescribers of opioid and sedative therapy
    - Patients with a prior history of sedative poisoning

Background:

The Substance Use Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities (SUPPORT) Act was signed into law on October 24, 2018 by President Trump.[3] This law requires state Medicaid programs to have drug utilization review safety edits for opioid refills and an automated claims review process to identify refills in excess of state defined limits, monitor concurrent prescribing of opioids and benzodiazepines or antipsychotics, and require managed care plans to have these processes in place by October 1, 2019.[3] The FDA issued an alert regarding safety issues associated with concomitant use of opioids with drugs that depress the central nervous system (CNS) in 2016.[1] An FDA review found combined use of opioid medicines with benzodiazepines or other CNS depressants has resulted in serious side effects, including slowed or difficult breathing and deaths.[1] The FDA recommended health care professionals should limit prescribing opioid pain medicines with benzodiazepines or other CNS depressants only to patients for whom alternative treatment options are inadequate.[1] If these medicines are prescribed together, the dosages and duration of each drug should be limited to the minimum possible while achieving the desired clinical effect.[1] The specific CNS depressants identified by the FDA are listed in **Appendix 3, Table A5.**

Concomitant Use of Opioids and Benzodiazepines

Two studies were identified that showed an increased trend in concomitant dispensing of opioid analgesics and benzodiazepines, and an increased frequency of combined benzodiazepine and prescription opioid misuse, abuse, and overdose, as measured by national emergency department (ED) visit and overdose death rates (from prescribed or greater than prescribed doses).[4] The first publication, a time series study, examined concomitant use patterns of opioid analgesics and benzodiazepines in United States (U.S.) outpatient retail settings.[4] Between 2002 and 2014, the annual number of patients dispensed an opioid analgesic increased 8 percent, from 75 million to 81 million, and the annual number of patients dispensed a benzodiazepine increased 31 percent, from 23 million to 30 million.[4] During this period, the proportion of opioid analgesic recipients receiving an overlapping benzodiazepine prescription increased by 41 percent, which translates to an increase of more than 2.5 million opioid analgesic users receiving concomitant benzodiazepines in 2014, compared to 2002.[4] Approximately half of these patients received both prescriptions from the same prescriber on the same day.[4] The patients with the highest probability of receiving concomitant prescriptions were women, patients older than 65, and chronic users of opioid analgesics (patients receiving opioids for 90 days or greater).[4] This study evaluated co-prescribing trends of opioids and benzodiazepines, but did not evaluate adverse event outcomes.

The second study used the Drug Abuse Warning Network (DAWN) to analyze ED visits due to nonmedical use of both prescription opioid analgesics and benzodiazepines, and the National Vital Statistics System Multiple Cause-of-Death file to analyze drug overdose deaths involving both prescription opioid analgesics and benzodiazepines.[5] Between 2004 and 2011, the rate of nonmedical use-related ED visits involving both opioid analgesics and benzodiazepines increased from 11 to 34.2 per 100,000 population (p-trend <0.0001).[5] During this same time period, drug overdose deaths, from taking prescribed or greater than prescribed doses and involving both opioid analgesics and benzodiazepines, increased from 0.6 to 1.7 per 100,000 (p-trend <0.0001).[5] The proportion of prescription opioid analgesic overdose deaths in which benzodiazepines were also implicated increased from 18 percent to 31 percent during this time period (p-trend <0.0001).[5]

Two additional studies provide additional evidence of increased risk of adverse events occurring in patients dispensed both opioid analgesics and benzodiazepines. A prospective observational cohort study conducted in North Carolina found the rates of overdose death among patients co-dispensed opioid analgesics and benzodiazepines were 10 times higher (7.0 per 10,000 person-years; 95% confidence interval [CI] 6.3-7.8) than among patients dispensed opioid analgesics alone (0.7 per 10,000 person-years; 95% CI 0.6-0.9).[6] A case-cohort study examined the Veterans Health Administration data from 2004-2009 and found the risk of death from drug overdose increased among those with concomitant opioid analgesic and benzodiazepine prescriptions.[7] Compared to patients taking opioid analgesics with no history of a benzodiazepine prescription, patients taking opioid analgesics with a history of a benzodiazepine prescription had an increased risk of fatal overdose (hazard ratio [HR]=2.33; 95% CI: 2.05-2.64), and those with a current benzodiazepine prescription had a similarly increased risk (HR=3.86; 95% CI: 3.49-4.26) for fatal overdose.[7] In addition, the risk of drug overdose death increased as the daily benzodiazepine dose increased.[7]

Based on the trends of increased concomitant use of opioid analgesics and benzodiazepines as well as increased harms associated with concomitant use described in these four studies, the FDA required a new boxed warning to be added to the labeling of opioid analgesics, opioid cough medications and benzodiazepines in 2016.[1]

Concomitant Use of Opioids and other CNS depressants

Recent studies show that concomitant use of opioid analgesics and CNS depressants other than benzodiazepines, including alcohol, is also associated with serious adverse events. One study analyzed the involvement of CNS depressants (including barbiturates, antipsychotic and neuroleptic drugs, antiepileptic and antiparkinsonian drugs, anesthetics, autonomic nervous system drugs, and muscle relaxants) and found that these CNS depressants were contributory to death in many cases where opioid analgesics were also implicated.[2] Opioids were involved in the majority of deaths involving benzodiazepines (77.2%), antiepileptic and antiparkinsonism drugs (65.5%), antipsychotic and neuroleptic drugs (58.0%), antidepressants (57.6%), other analgesics, antipyretics, and antirheumatics (56.5%), and other psychotropic drugs (54.2%).[2] A second study analyzed 2010 DAWN data and found that alcohol was involved in 18.5 percent of opioid analgesic abuse-related ED visits and 22.1 percent of opioid analgesic-related deaths.[8] All of the studies were based on opioid analgesics; however, because of similar pharmacologic properties, the FDA noted it is reasonable to expect similar risks with concomitant use of opioid cough medications and benzodiazepines, other CNS depressants, or alcohol.[1] Based on these studies, the FDA recommended the boxed warning for opioid analgesics and opioid cough medications also highlight the risk of concomitant use with other CNS depressants.[1]

Concomitant use of Medication Assisted Treatment (MAT) and CNS depressants

An FDA drugs safety communication issued in 2017 cautioned about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants.[9] The FDA advises that the opioid addiction medications buprenorphine and methadone should not be withheld from patients taking benzodiazepines or other CNS depressants.[9] The combined use of these drugs increases the risk of serious side effects; however, the harm caused by untreated opioid addiction can outweigh these risks.[9] Careful medication management by health care professionals can reduce these risks.[9] The FDA required this

information to be added to the buprenorphine and methadone drug labels along with detailed recommendations for minimizing the use of medication-assisted treatment (MAT) drugs and benzodiazepines together.[9]

Methods:
The patient population included current Medicaid patients (FFS and CCO) with an opioid index event from 4/1/2017 to 3/31/2018 and at least one claim for an additional sedating medication within the 4 months before or after then index event. Patients with Medicare or with only limited Medicaid drug coverage were excluded from the analysis (benefit plans: BMM, BMD, CWM, MED, MND, SMF, SMB). Patients with less than 75% Medicaid eligibility in the 6 months following the index event were excluded in order to ensure complete data was captured for included patients.

Definitions used for the analysis:

- The **index event** was defined as the first paid pharmacy claim for an opioid. Opioids from the following PDL classes were included in the analysis: Opioids, short-acting; Opioids, long-acting; and Cough and Cold (see **Appendix 3 Table A1**).
- **Concomitant sedative therapy** was assessed for the drugs listed in **Table A2**. They included pharmacy claims for benzodiazepines, sedative for insomnia, muscle relaxants, and antipsychotics. Concomitant sedating therapy was defined as at least 6 weeks of overlapping therapy with no more than a 7 day gap in coverage. Length of concomitant sedative therapy was defined as short-term (6-12 weeks) or long-term (>12 weeks). Type of concomitant sedative therapy was categorized by drug class and included both CCO and FFS claims. The total number of unique sedating drugs with overlapping therapy for these timeframes was also evaluated.
- **FFS and CCO utilization:** Patients were categorized according to the payer (FFS or CCO) of the opioid index event. In order to assess the number of patients with both FFS and CCO claims, patients were evaluated for sedative therapy in the 30 days before or after the index event. Patients were categorized according to the type of claim for the index event (FFS or CCO). All prior and subsequent claims for any sedative were evaluated in the 30 days before and after the index event. If patients were enrolled in both FFS and a CCO within this timeframe they may be counted more than once. Sedative therapy was categorized according to the claim type (FFS or CCO).
- **Duration of opioid or other sedative therapy** was assessed using proportion of days covered (PDC) in the 6 months following the index event. PDC was divided into 4 categories: a PDC of up to 16% (corresponding to approximately 1 month of treatment), PDC of 16-33% (1-2 months), PDC of 34-67% (2-4 months) and PDC greater than 67% (>4 months).
- **Prescriber type**: Prescribers of patients with combination opioid and sedative therapy were identified using the primary provider taxonomy associated with overlapping claims of concomitant opioids and sedatives. Patients were also categorized according to the number of unique providers involved in prescribing opioid and sedating medications in the 6 months following the index event and the number of unique providers who prescribe overlapping sedative and opioid therapy.
- **Hospitalizations, emergency department visits**, and patients with visits associated with a **sedative poisonings or adverse effects** were identified using codes shown in **Table A3** and diagnoses associated with sedative poisonings or adverse events listed in **Table A4**. Medical visits may be associated with more than one diagnosis and both primary and secondary diagnoses were included in the analysis. Two analyses were conducted.
    - The first analysis evaluates unique patients who had a hospital visit or ER visit in the 6 months following the index event. The number of patients is reported for the overall population (every patient with an IE) and for various patient groups in order to evaluate what patients may be at higher risk of sedative adverse events. Using this method avoids counting patients multiple times, but it may also potentially miss valuable information in patients with multiple medical visits.
    - A second analysis evaluated all hospitalizations or ER visits associated with a diagnosis of sedative poisoning or adverse events in the pre-specified population. Pharmacy claims paid for before the medical visit were evaluated to identify prescribing patterns which may be associated with more frequent visits. This analysis captures all ED visits or hospitalizations for sedative poisonings for patients during the study period, and

patients would be counted more than once if they had multiple medical visits. Subsequently, data for this analysis may be more heavily influenced by members with frequent ED visits or hospitalizations for sedative poisoning.

Results:

Demographics for patients prescribed opioid and sedative therapy is presented in **Table 1**. The majority of patients prescribed opioids and sedatives are white, female adults. Overall, 92% of patients were enrolled in a CCO at the time of the index event and only 4% of the population had a change in enrollment within 45 days of their opioid prescription. In total, over 48,000 patients were identified as filling prescriptions for an opioid and some type of sedative therapy within 4 months each other. For patients prescribed a subsequent sedative prescription, the average time between the opioid and sedative prescription was 29 days. In only 27% of patients prescribed both opioids and sedatives, sedative therapy was separated by more than 30 days from the time of the opioid prescription.

Table 1. Demographics for patients prescribed opioid and sedative therapy

	N=	48,186	%
Age			
Average (min - max)		41.9	(0-88)
<=18		1,317	2.7%
19-60		44,643	92.6%
>60		2,226	4.6%
Female		32,183	66.8%
Race			
White		26,051	54.1%
Hispanic		893	1.9%
African American		1,207	2.5%
Native American		2,517	5.2%
Enrollment at Index			
CCO		44,467	92.3%
FFS		3,719	7.7%
Change in enrollment within 45 days		2,066	4.3%
Average days to 1st subsequent sedative claim		29	(0-184)

Table 2 describes the frequency in which patients are prescribed opioids and sedative from both FFS and a CCO within one month before or after the opioid index event. In the majority of Medicaid members, both prescriptions were billed to the same entity (either FFS or a CCO). In FFS, 50-53% of patients received sedative therapy from FFS within 30 days before or after an opioid prescription. Only 9% had a subsequent sedative claim paid for by a CCO within 30 days. For members enrolled in a CCO, approximately 41% had a sedative claim paid by a CCO within the previous or subsequent 30 days. However, because mental health medications like antipsychotics and benzodiazepines are carved-out and paid for by FFS, a significant number of patients enrolled in a CCO have claims for

sedative therapy paid for by FFS. Of over 44,000 CCO patients with a paid opioid prescription, 25% had a paid FFS claim for sedative therapy in the 30 days before the opioid and 25% had a subsequent FFS sedative claim in the 30 days after the member was prescribed an opioid.

Table 2. Patients with at least one claim for sedative therapy in the 30 days before or after the index event. Patients were categorized according to the payer (FFS or CCO) for the index event. All prior and subsequent claims for a sedative were evaluated in the 30 days before and after the index event. Categories are not mutually exclusive. If patients were enrolled in both FFS and a CCO within this timeframe they may be counted more than once.

	FFS index event		CCO Index Event	
N=	**3,719**	**%**	**44,467**	**%**
Patients with a subsequent sedative claim	2,221	59.7%	26,141	58.8%
Subsequent sedative FFS claims	2,002	53.8%	11,000	24.7%
Subsequent sedative CCO claims	346	9.3%	18,309	41.2%
Patients with a prior history of sedative use	1,915	51.5%	26,171	58.9%
Prior sedative FFS claims	1,868	50.2%	11,291	25.4%
Prior sedative CCO claims	62	1.7%	18,040	40.6%

The majority of patients (61-65%) prescribed opioid therapy had a PDC of less than 16% (less than approximately 30 days) in the 6 months after the opioid index event (**Table 3**). About 16% of patients with claims for sedating medication had a PDC of more than 67% (or approximately 120 days). Almost 5,400 patients (~12% of patients prescribed opioid therapy) had overlapping claims for a sedative medication. Most patients with overlapping claims were prescribed long-term opioid and sedative therapy with a PDC of more than 67% for overlapping therapy in the 6 months following the index event. **Table 4** further describes patients who were prescribed continuous concomitant opioid and sedative therapy for more than 6 weeks. In most circumstances combination therapy included muscle relaxants and benzodiazepines. The majority of patients (80-94%) prescribed combination opioid-sedative therapy for more than 6 weeks were prescribed only one sedating medication in conjunction with an opioid.

Table 3. Proportion of covered days for patients prescribed opioid or other sedative therapy in the 6 months following the index event. For combination therapy the PDC describes the number of days covered by both an opioid and another sedative therapy.

	FFS IE		CCO IE	
	3,719	**%**	**44,467**	**%**
PDC of opioid therapy				
<=16%	2,275	61.2%	29,140	65.5%
17-33%	473	12.7%	4,452	10.0%
34-67%	389	10.5%	3,494	7.9%
>67%	582	15.6%	7,381	16.6%

PDC of any other sedative therapy (includes only patients prescribed subsequent sedative therapy)				
<=16%	1,244	33.4%	13,099	29.5%
17-33%	786	21.1%	7,990	18.0%
34-67%	541	14.5%	6,392	14.4%
>67%	679	18.3%	10,563	23.8%
PDC of opioid and another sedative therapy (includes only patients prescribed overlapping opioid and sedative prescriptions)				
<=16%	20	0.5%	209	0.5%
17-33%	118	3.2%	1,238	2.8%
34-67%	174	4.7%	1,804	4.1%
>67%	123	3.3%	2,141	4.8%

Table 4. Duration of concomitant opioid and sedative therapy. Type of combination sedative therapy was defined according to drug class.

	Short-term concomitant therapy (6-12 weeks)		**Long-term concomitant therapy (>12 weeks)**	
Total	**2,832**	**%**	**2,886**	
Sedative Class				
Antipsychotic	625	22.1%	608	21.1%
Barbiturate	9	0.3%	8	0.3%
Benzodiazepine	848	29.9%	1,026	35.6%
Muscle Relaxant	1,837	64.9%	1,579	54.7%
Sedative	324	11.4%	289	10.0%
Number of unique sedating drugs prescribed in combination with an opioid				
1	2,650	93.6%	2,302	79.8%
2	443	15.6%	499	17.3%
3	89	3.1%	82	2.8%
4	10	0.4%	16	0.6%
5	2	0.1%	2	0.1%

Prescribers involved in prescribing combination opioid and sedative medications for more than 6 weeks are listed in **Table 5**. Physicians account for over 75% of concomitant overlapping opioid and sedative claims. Advanced practice nurses, physician assistants, and mental health providers also account for a significant proportion of prescribed combination therapy. In many cases multiple prescribers are involved in prescribing opioids and sedating medications. Only 43% of patients prescribed overlapping treatment for 6-12 weeks and 35% of patients prescribed combination treatment for more than 12 weeks received both the opioid and sedative from a single provider. Less than 15% of patients had more than 3 providers prescribing combination sedating and opioid therapy.

Table 5. Prescriber characteristics Prescriber types stratified primary provider taxonomy which were associated with claims for overlapping combination treatment with opioids and sedatives.

		Short-term concomitant therapy (6-12 weeks)		Long-term concomitant therapy (>12 weeks)	
		2,832	**%**	**2,886**	
Patient counts for Top 10 prescriber types associated with claims for concomitant overlapping sedative therapy					
1	Physician	2,126	75.1%	2,296	79.6%
2	Advance Practice Nurse	1,025	36.2%	1,132	39.2%
3	Physician Assistants	728	25.7%	767	26.6%
4	MH Provider	307	10.8%	369	12.8%
5	Dentist	80	2.8%	74	2.6%
6	Adv Comp Health Care	72	2.5%	90	3.1%
7	Podiatrist	12	0.4%	12	0.4%
8	Nurse	9	0.3%	4	0.1%
9	Chiropractor	2	0.1%	1	0.0%
10	Pharmacist	1	0.0%	1	0.0%
Patient counts by number of prescribers associated with claims for overlapping sedative therapy					
1		1,215	42.9%	1,002	34.7%
2		976	34.5%	971	33.6%
3		398	14.1%	518	17.9%
4		136	4.8%	223	7.7%
5		64	2.3%	110	3.8%
6		27	1.0%	40	1.4%
7		8	0.3%	12	0.4%
8		4	0.1%	5	0.2%
9		3	0.1%	3	0.1%
≥10		1	0.0%	1	0.0%

The overall incidence of hospitalization or emergency department visits due to sedative poisoning or adverse events was small and occurred in only 0.6% of patients prescribed opioids and sedatives (**Table 6**). The duration of therapy did not demonstrate consistent trends for incidence of hospitalization, emergency department visits and sedative poisonings. However, patients prescribed sedatives and opioids from 3 or more prescribers and patients with a prior history of sedative overdose had a slightly higher incidence compared to the total population (2.5% and 5.5%, respectively). Similarly, all cause emergency department visits and hospitalizations occurred with higher frequency in patients with prescriptions from multiple providers and those with a prior history of sedative poisoning.

Table 6. Patient groups associated with hospitalization, emergency department visit, or visits with a diagnosis of sedative overdose or adverse effects in the 6 months following the index event. Percentages are calculated as a proportion of each group.

As Percent of Group	Total Patients in Each Category	Patients with Hospitalization		Patients with ED Visit		Patients with Hospitalization or ED Visit due to sedative poisoning or adverse effects	
All patients with IE	48,186	4,713	9.8%	22,907	47.5%	312	0.6%
Patients with no concomitant sedative therapy (< 6 weeks)	42,468	4,115	9.7%	20,794	49.0%	272	0.6%
Patients with short-term (6-12 weeks) concomitant sedative therapy	2,832	382	13.5%	1,231	43.5%	23	0.8%
Patients with long-term (>12 weeks) concomitant sedative therapy	2,886	256	8.9%	1,053	36.5%	18	0.6%
Number of prescribers of sedative therapy in the 6 months after the IE							
1	26,450	1,993	7.5%	11,434	43.2%	95	0.4%
2	9,969	1,191	11.9%	5,395	54.1%	69	0.7%
>=3	4,874	1,117	22.9%	3,285	67.4%	**123**	**2.5%**
Patients with a history of prior sedative poisoning or adverse event in the 1 year before the IE	889	192	21.6%	590	66.4%	**49**	**5.5%**

Prescribing patterns for patients with a hospitalization or emergency department visit for sedative poisoning or sedative adverse events were also evaluated prior to each event on a visit by visit basis. **Table 7** shows prescribing patterns in the 120 days prior to each visit. Only 13-16% of visits for sedative poisoning occurred when patients received prescriptions written from a single provider in the 120 days before the event. For approximately 27% of visits, patients had prescriptions from 2 providers, and over 50% of visits occurred when patients filled prescriptions from 3 or more providers in the prior 120 days. There was no apparent pattern based on the type or number of prescribed agents.

Table 7. ED or hospital visits associated with a diagnosis of sedative poisoning or adverse events. Claims for opioids and sedatives were assessed 120 days before each visit.

	Hospital Visit		ED Visit	
N = number of visits =	**141**	**%**	**334**	**%**
Paid prescriptions prior to the visit				
Naloxone	5	3.5%	5	1.5%
Benzodiazepine	70	49.6%	166	49.7%
Antipsychotic	67	47.5%	143	42.8%
Opioid	122	86.5%	296	88.6%
Sedative, muscle relaxant, or barbiturate	87	61.7%	184	55.1%
Opioid and benzodiazepine	66	46.8%	153	45.8%
Opioid and antipsychotic	59	41.8%	130	38.9%
Opioid and either sedative, muscle relaxant, or barbiturate	76	53.9%	166	49.7%
Number of prescribers of opioid and sedative therapy				
1	19	13.5%	54	16.2%
2	39	27.7%	90	26.9%
>=3	81	57.4%	179	53.6%
Number of unique sedating agents (based on HSN)				
1	48	34.0%	119	35.6%
2	39	27.7%	92	27.5%
>=3	45	31.9%	88	26.3%

Limitations:

Data presented in this report are based on Medicaid claims history which have several inherent limitations. For example, information on provider type may be inaccurate, out-of-date, or incomplete for some providers, and prescribers with multiple specialties or designations may not be identified. In addition, use of PDC attempts to estimate the frequency which a patient takes a prescription, but accuracy of this method has not been validated, and patients may not always be categorized appropriately. Similarly, information based on diagnosis of sedative poisoning or overdose may be delayed, incomplete, or inaccurate. This data only captures patients who have a hospital encounter (either a hospital admission or emergency department visit) as a result of sedative poisoning. It is likely that a significant proportion of patients who do not receive hospital services for sedative overdose are not captured with these data. Similarly, while data indicate patients prescribed opioids and sedatives from multiple prescribers may have a higher risk of sedative overdose, the data is observational and based on a small proportion of patients. There may be multiple confounding factors which contribute to higher risk of overdose in these populations and cause and effect relationships or statistical significance between populations cannot be determined.

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1. FDA Drug Safety Communication: FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning. https://www.fda.gov/Drugs/DrugSafety/ucm518473.htm. Accessed March 20, 2019.
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HEALTH SYSTEMS DIVISION
Provider Services
500 Summer St NE
Salem, OR 97301

Date issued: <July 1, 2019>

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»

Subject: Concurrent Prescribing of Opioids and CNS Depressants
for <Patient Name>
ID: XXXXXXX DOB: <MM/DD/YYYY>

Dear Prescriber:

The Oregon Health Plan Fee-for-Service (OHP-FFS) pharmacy program reviews the dispensing of outpatient prescription medications to ensure medically appropriate and safe use.

What is the concern?

OHP-FFS pharmacy paid claims data indicate that your patient recently filled a prescription for **<Drug A>** in combination with another sedating agent from a different prescriber which is still active on the patient's profile.

Concomitant use of opioids with other CNS depressants (benzodiazepines, gabapentinoids, antipsychotics, etc) greatly increases patient risk of hypotension, profound sedation, coma, or fatal respiratory depression.[1]

What should you do?

- Consider prescribing naloxone in patients with high risk for overdose
- Check the Oregon PDMP to evaluate co-prescribing of opioids with other sedatives
- Consider tapering or discontinuing your patient's chronic opioid and/or CNS depressant therapy whenever risks (e.g. sedation, dependence, cognitive dysfunction and/or psychiatric instability) outweigh benefits. An opioid taper guide may be found here: https://www.cdc.gov/drugoverdose/pdf/clinical_pocket_guide_tapering-a.pdf.[2]

For more information, feel free to check the box below:

☐ **Please send me a copy of my patient's recent pharmacy claims history → FAX to (503) 945-xxxx)**

Questions?

For pharmacy point of sale questions, you may call the Oregon Pharmacy Call Center at 888-202-2126.

References:

1. FDA Drug Safety Communication: FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning. https://www.fda.gov/Drugs/DrugSafety/ucm518473.htm. Accessed March 20, 2019.
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Appendix 2: Retrospective DUR Inclusion/Exclusion Criteria and Reporting Parameters

Inclusion criteria:

- Patients currently enrolled in Medicaid (either fee-for-service [FFS] or a coordinated care organization [CCO]) AND
- Patients prescribed both an opioid and another sedating medication (as defined above) within the past 120 days AND
- At least one of the following characteristics:
    - Patients with prescriptions for opioids and sedatives which overlap by at least 7 days written by more than one provider OR
    - Patients with prescriptions for opioids and sedatives from 3 or more unique providers in the past 120 days OR
    - Members with a history of sedative poisoning or adverse events within the past 2 years

Exclusion criteria:

Exclude patients meeting any of the following criteria:

- Patients not currently enrolled in Medicaid
- Patients who have been had a letter sent within the past 3 months
- Providers who have been messaged for the same patient within the past 12 months

The prescriber of the most recent sedative or opioid prescription will receive the provider letter.

Reporting Parameters

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

- Patients identified
- Prescribers identified
- Prescribers successfully notified
- Patients with discontinuation of therapy within the next 90 days (discontinuation defined as no new prescriptions filled for the drug class)
    - Opioid
    - Benzodiazepine
    - Antipsychotic
- Patients with a new prescription for naloxone within the next 90 days
- Average number of sedative drugs dispensed within the next 90 days
- Average number of sedative prescribers writing prescriptions in the next 90 days

Appendix 3

Table A1. Codes for Opioid Analgesics

Class	HSN	Generic
Cough and Cold	035501	bromphenira/pseudoephed/codein
Cough and Cold	035361	brompheniramine/p-eph/codeine
Cough and Cold	036713	chlorphen/pseudoephed/codeine
Cough and Cold	000347	chlorpheniramine/codeine phos
Cough and Cold	037229	chlorpheniramine/PE/codeine

Cough and Cold	000206	codeine phosphate/guaifenesin
Cough and Cold	009011	codeine phosphate/pyrilamine
Cough and Cold	000348	codeine poli/chlorphenir polis
Cough and Cold	035645	dexchlorphen/phenyleph/codeine
Cough and Cold	000209	guaifenesin/hydrocodone
Cough and Cold	039314	hydrocodone bit/homatrop me-br
Cough and Cold	000352	hydrocodone/chlorphen p-stirex
Cough and Cold	000487	hydrocodone/cpm/pseudoephed
Cough and Cold	000265	hydrocodone/pseudoephed/guaif
Cough and Cold	000419	PE/codeine/acetaminophen/cpm
Cough and Cold	000424	phenyleph/hydrocodon/pyrilamin
Cough and Cold	000421	phenylephrine HCl/cod/pyril
Cough and Cold	000334	phenylephrine/cod/cpm/pot iod
Cough and Cold	035441	phenylephrine/codeine/guaifen
Cough and Cold	000425	phenylephrine/hydrocodone/cpm
Cough and Cold	000277	pot guaiaco/hydrocodone
Cough and Cold	000345	promethazine HCl/codeine
Cough and Cold	000420	promethazine/phenyleph/codeine
Cough and Cold	000484	pseudoephed/cod/chlorphenir
Cough and Cold	035174	pseudoephed/codeine/guaifen
Cough and Cold	005359	pseudoephed/codeine/triprolidn
Cough and Cold	000488	pseudoephed/hydrocodone
Cough and Cold	042426	triprolidine/phenyleph/codeine
Opioids, Long-Acting	001731	hydrocodone bitartrate
Opioids, Long-Acting	001695	hydromorphone HCl
Opioids, Long-Acting	001743	levorphanol tartrate
Opioids, Long-Acting	001745	methadone HCl
Opioids, Long-Acting	001694	morphine sulfate
Opioids, Long-Acting	036577	morphine sulfate/naltrexone
Opioids, Long-Acting	001742	oxycodone HCl
Opioids, Long-Acting	043376	oxycodone myristate
Opioids, Long-Acting	001696	oxymorphone HCl
Opioids, Long-Acting	036411	tapentadol HCl
Opioids, Long-Acting	008317	tramadol HCl
Opioids, Short-Acting	001717	acetaminophen with codeine

Opioids, Short-Acting	001739	acetaminophen/caff/dihydrocod
Opioids, Short-Acting	034574	aspirin/caffein/dihydrocodeine
Opioids, Short-Acting	001734	aspirin/caffeine/dihydrocodein
Opioids, Short-Acting	001711	aspirin/codeine phosphate
Opioids, Short-Acting	044795	benzhydrocodone/acetaminophen
Opioids, Short-Acting	001713	butalbit/acetamin/caff/codeine
Opioids, Short-Acting	001702	cod/ASA/salicylmd/acetamin/caf
Opioids, Short-Acting	001722	codeine sulfate
Opioids, Short-Acting	001699	codeine/butalbital/ASA/caffein
Opioids, Short-Acting	001727	hydrocodone bitartrate/aspirin
Opioids, Short-Acting	001730	hydrocodone/acetaminophen
Opioids, Short-Acting	014296	hydrocodone/ibuprofen
Opioids, Short-Acting	001695	hydromorphone HCl
Opioids, Short-Acting	026757	ibuprofen/oxycodone HCl
Opioids, Short-Acting	001687	meperidine HCl
Opioids, Short-Acting	001694	morphine sulfate
Opioids, Short-Acting	001742	oxycodone HCl
Opioids, Short-Acting	001741	oxycodone HCl/acetaminophen
Opioids, Short-Acting	004576	oxycodone HCl/aspirin
Opioids, Short-Acting	001696	oxymorphone HCl
Opioids, Short-Acting	001781	pentazocine HCl/naloxone HCl
Opioids, Short-Acting	001769	propoxyphene HCl
Opioids, Short-Acting	001767	propoxyphene HCl/acetaminophen
Opioids, Short-Acting	001768	propoxyphene nap/acetaminophen
Opioids, Short-Acting	001763	propoxyphene/aspirin/caffeine
Opioids, Short-Acting	036411	tapentadol HCl
Opioids, Short-Acting	008317	tramadol HCl
Opioids, Short-Acting	022880	tramadol HCl/acetaminophen

Table A2. Codes for Concomitant Sedating Medications

Class	HSN	Generic
Antipsychotics, 1st Gen	001621	chlorpromazine HCl
Antipsychotics, 1st Gen	001626	fluphenazine HCl
Antipsychotics, 1st Gen	001662	haloperidol
Antipsychotics, 1st Gen	001661	haloperidol lactate

Antipsychotics, 1st Gen	039886	loxapine
Antipsychotics, 1st Gen	001664	loxapine succinate
Antipsychotics, 1st Gen	001627	perphenazine
Antipsychotics, 1st Gen	001637	pimozide
Antipsychotics, 1st Gen	001631	thioridazine HCl
Antipsychotics, 1st Gen	001668	thiothixene
Antipsychotics, 1st Gen	001667	thiothixene HCl
Antipsychotics, 1st Gen	001630	trifluoperazine HCl
Antipsychotics, 2nd Gen	024551	aripiprazole
Antipsychotics, 2nd Gen	036576	asenapine maleate
Antipsychotics, 2nd Gen	042283	brexpiprazole
Antipsychotics, 2nd Gen	042552	cariprazine HCl
Antipsychotics, 2nd Gen	004834	clozapine
Antipsychotics, 2nd Gen	037321	lurasidone HCl
Antipsychotics, 2nd Gen	011814	olanzapine
Antipsychotics, 2nd Gen	034343	paliperidone
Antipsychotics, 2nd Gen	043373	pimavanserin tartrate
Antipsychotics, 2nd Gen	014015	quetiapine fumarate
Antipsychotics, 2nd Gen	008721	risperidone
Antipsychotics, 2nd Gen	021974	ziprasidone HCl
Benzodiazepines	001617	alprazolam
Benzodiazepines	001656	amitriptyline/chlordiazepoxide
Benzodiazepines	001611	chlordiazepoxide
Benzodiazepines	001610	chlordiazepoxide HCl
Benzodiazepines	002037	chlordiazepoxide/clidinium Br
Benzodiazepines	001894	clonazepam
Benzodiazepines	001612	clorazepate dipotassium
Benzodiazepines	001615	diazepam
Benzodiazepines	004846	lorazepam
Benzodiazepines	001616	oxazepam
Muscle Relaxants, Oral	001949	baclofen
Muscle Relaxants, Oral	001944	carisoprodol
Muscle Relaxants, Oral	001942	carisoprodol/aspirin
Muscle Relaxants, Oral	001720	carisoprodol/aspirin/codeine
Muscle Relaxants, Oral	001941	chlorzoxazone

Muscle Relaxants, Oral	001950	cyclobenzaprine HCl
Muscle Relaxants, Oral	001947	dantrolene sodium
Muscle Relaxants, Oral	001945	metaxalone
Muscle Relaxants, Oral	001938	methocarbamol
Muscle Relaxants, Oral	001936	methocarbamol/aspirin
Muscle Relaxants, Oral	001906	orphenadrine citrate
Muscle Relaxants, Oral	001791	orphenadrine/aspirin/caffeine
Muscle Relaxants, Oral	011582	tizanidine HCl
Sedatives	004480	diphenhydramine HCl
Sedatives	001650	doxepin HCl
Sedatives	004482	doxylamine succinate
Sedatives	006036	estazolam
Sedatives	026791	eszopiclone
Sedatives	001593	flurazepam HCl
Sedatives	001619	midazolam HCl
Sedatives	045030	midazolam/ketamine/ondansetron
Sedatives	001595	quazepam
Sedatives	033126	ramelteon
Sedatives	041333	suvorexant
Sedatives	040927	tasimelteon
Sedatives	001592	temazepam
Sedatives	001594	triazolam
Sedatives	020347	zaleplon
Sedatives	007842	zolpidem tartrate
Barbiturate	001566	butabarbital sodium
Barbiturate	001570	secobarbital sodium
Barbiturate	001561	phenobarbital

Table A3. Health Outcome Codes

ED Visits	Procedure Codes OR Revenue Center Codes	99281-99285, 99288 0450-0459 or 0981
Hospitalizations	Claim Type = I	Claim Type = I

Table A4. Diagnosis codes associated with sedative poisoning or adverse effects

ICD-10 code	Description
T42.3X1xx-T42.3X5xx	Poisoning by, adverse effect of barbiturates
T42.4X1xx-T42.4X5xx	Poisoning by, adverse effect of benzodiazepines
T42.6X1xx-T42.6X5xx	Poisoning by, adverse effect of other antiepileptic and sedative-hypnotic drugs
T42.7X1xx-T42.7X5xx	Poisoning by, adverse effect of unspecified antiepileptic and sedative-hypnotic drugs
T42.8X1xx-T42.8X5xx	Poisoning by, adverse effect of antiparkinsonism drugs and other central muscle-tone depressants
T40.0X1xx-T40.0X5xx	Poisoning by, adverse effect of opium
T40.1X1xx-T40.1X5xx	Poisoning by, adverse effect of heroin
T40.2X1xx-T40.2X5xx	Poisoning by, adverse effect of other opioids
T40.3X1xx-T40.3X5xx	Poisoning by, adverse effect of methadone
T40.4X1xx-T40.4X5xx	Poisoning by, adverse effect of synthetic narcotics
T40.601xx-T40.605xx	Poisoning by, adverse effect of other and unspecified narcotics
T40.691xx-T40.695xx	Poisoning by, adverse effect of other narcotics
T48.1X1xx-T48.1X5xx	Poisoning by, adverse effect of skeletal muscle relaxants [neuromuscular blocking agents]
T48.3X1xx-T48.3X5xx	Poisoning by, adverse effect of antitussives
T48.5X1xx-T48.5X5xx	Poisoning by, adverse effect of other anti-common-cold drugs
T48.901xx-T48.905xx	Poisoning by, adverse effect of unspecified agents primarily acting on the respiratory system
T48.991xx-T48.995xx	Poisoning by, adverse effect of other agents primarily acting on the respiratory system
T43.3X1xx-T43.3X5xx	Poisoning by, adverse effect of phenothiazine antipsychotics and neuroleptics
T43.4X1xx-T43.4X5xx	Poisoning by, adverse effect of butyrophenone and thiothixene neuroleptics
T43.501xx-T43.505xx	Poisoning by, adverse effect of unspecified antipsychotics and neuroleptics
T43.591xx-T43.595xx	Poisoning by, adverse effect of other antipsychotics and neuroleptics
T43.8X1xx-T43.8X5xx	Poisoning by, adverse effect of other psychotropic drugs
T43.9X1xx-T43.9X5xx	Poisoning by, adverse effect of unspecified psychotropic drug

Table A5. List of Benzodiazepines and Other CNS depressants identified by the FDA*[1]

Generic Name	Brand Name(s)
Benzodiazepines	
alprazolam	Xanax, Xanax XR
chlordiazepoxide	Librium, Librax
clobazam	Onfi
clonazepam	Klonopin
clorazepate	Gen-Xene, Tranxene
diazepam	Diastat, Diastat Acudial, Valium
estazolam	No brand name currently marketed
flurazepam	No brand name currently marketed

lorazepam	Ativan
oxazepam	No brand name currently marketed
quazepam	Doral
temazepam	Restoril
triazolam	Halcion
Other Sleep Drugs and Tranquilizers	
butabarbital sodium	Butisol
eszopiclone	Lunesta
pentobarbital	Nembutal
ramelteon	Rozerem
secobarbital sodium	Seconal sodium
suvorexant	Belsomra
zaleplon	Sonata
zolpidem	Ambien, Ambien CR, Edluar, Intermezzo, Zolpimist
Muscle Relaxants	
baclofen	Gablofen, Lioresal
carisoprodol	Soma, Soma Compound, Soma Compound w/ codeine
chlorzoxazone	No brand name currently marketed
cyclobenzaprine	Amrix
dantrolene	Dantrium, Revonto, Ryanodex
metaxalone	Skelaxin
methocarbamol	Robaxin, Robaxin-750
orphenadrine	No brand name currently marketed
tizanidine	Zanaflex
Antipsychotics	
aripiprazole	Abilify, Abilify Maintena, Aristada
asenapine	Saphris
cariprazine	Vraylar
chlorpromazine	No brand name currently marketed
clozapine	Clozaril, Fazaclo ODT, Versacloz
fluphenazine	No brand name currently marketed
haloperidol	Haldol
iloperidone	Fanapt
loxapine	Adasuve
lurasidone	Latuda
molindone	No brand name currently marketed
olanzapine	Symbyax, Zyprexa, Zyprexa Relprevv, Zyprexa Zydis

paliperidone	Invega, Invega Sustenna, Invega Trinza
perphenazine	No brand name currently marketed
pimavanserin	Nuplazid
quetiapine	Seroquel, Seroquel XR
risperidone	Risperdal, Risperdal Consta
thioridazine	No brand name currently marketed
thiothixene	Navane
trifluoperazine	No brand name currently marketed
ziprasidone	Geodon

*****This is not a comprehensive list.

Table A6. List of Prescription Opioids and Cough Medicines identified by the FDA

Generic Name	**Found in Brand Name(s)**
alfentanil	Alfenta
buprenorphine	Belbuca, Buprenex, Butrans
butorphanol	No brand name currently marketed
codeine	Fioricet w/ codeine, Fiorinal w/ codeine, Soma Compound w/ codeine, Tylenol w/ codeine, Prometh VC w/ codeine (cough), Triacin-C (cough), Tuzistra-XR (cough)
dihydrocodeine	Synalgos-DC
fentanyl	Abstral, Actiq, Duragesic, Fentora, Ionsys, Lazanda, Sublimaze, Subsys
hydrocodone	Anexsia, Hysingla ER, Lortab, Norco, Reprexain, Vicodin, Vicoprofen, Zohydro ER, Flowtuss (cough), Hycofenix (cough), Obredon (cough), Rezira (cough), Tussicaps (cough), Tussigon (cough), Tussionex Pennkinetic (cough), Vituz (cough), Zutripro (cough)
hydromorphone	Dilaudid, Dilaudid-HP, Exalgo
meperidine	Demerol
methadone	Dolophine
morphine	Astramorph PF, Duramorph PF, Embeda, Infumorph, Kadian, Morphabond, MS Contin
oxycodone	Oxaydo, Oxycet, Oxycontin, Percocet, Percodan, Roxicet, Roxicodone, Xartemis XR
oxymorphone	Opana, Opana ER
pentazocine	Talwin
remifentanil	Ultiva
sufentanil	Sufenta
tapentadol	Nucynta, Nucynta ER
tramadol	Conzip, Ultracet, Ultram, Ultram ER

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Drug Class Update with New Drug Evaluation: Antidepressants

Date of Review: July 2019

Date of Last Review: November 2017
Dates of Literature Search: April 2019
Brand Name (Manufacturer): Spravato™ (Janssen)
Zulresso™ (Sage)
Dossiers Received: yes

Generic Name: esketamine
Generic Name: brexanolone

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

Purpose for Class Update:
This class update is primarily in response to the approval of two new antidepressants: esketamine (Spravato™) and brexanolone (Zulresso™). New high quality comparative efficacy and safety evidence on antidepressants published since the last update, presented in 2017, will also be evaluated and included.

Research Questions:
1. Is there new high-quality evidence demonstrating differences in efficacy or effectiveness between the different antidepressants or classes of antidepressants for major depressive disorder (MDD), generalized anxiety disorder (GAD) or other conditions?
2. Is there evidence demonstrating differences in harms data between the different antidepressants?
3. Are there subgroups of patients, based on demographics (e.g., age, race, sex, socio-economic factors), in which one antidepressant medication would be more effective or associated with less harm?
4. What is the evidence for efficacy and harms associated with esketamine and how does this compare to other antidepressants?
5. What is the evidence for efficacy and harms associated with brexanolone and how does this compare to other antidepressants?

Conclusions:
Depression
- Guidelines by the National Institute of Health and Care Excellence (NICE) recommend fluoxetine first-line in children and young people who require treatment with an antidepressant.[1]

Anxiety
- There is moderate strength of evidence that the treatment of children with imipramine or sertraline improve primary anxiety symptoms (which was considered a large treatment effect as assessed by standardized measurement) based on two good quality systematic reviews.[2,3]

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- An Agency for Healthcare Research and Quality (AHRQ) systematic review found moderate to high strength of evidence that serotonin-norepinephrine uptake inhibitors (SNRI) and selective serotonin reuptake inhibitors (SSRI) were effective in reducing the symptoms of anxiety in children, which was considered a moderate and large treatment effect, respectively.[3]
- Moderate quality evidence found a reduction in relapse for SSRIs, compared to placebo, in the treatment of social anxiety disorder as described in a 2017 Cochrane Systematic Review.[4] SNRIs were associated with a larger decrease in anxiety symptom scores compared to placebo, in this same population.[4]

Posttraumatic Stress Disorder

- An AHRQ review found moderate strength of evidence that fluoxetine, paroxetine, and venlafaxine are effective for reducing symptoms of posttraumatic stress disorder (PTSD) in adult patients.[5] Use of SSRIs and the SNRI, venlafaxine, for PTSD are also supported by NICE guidelines.[6]

Esketamine (Spravato)

- Esketamine nasal spray is indicated for treatment resistant depression and was found to be more effective than placebo in improving Montgomery-Asberg Depression Rating Scale (MADRS) scores with a mean difference of -4 points (95%CI, -7.3 to -0.64; P=0.020) at day 28 in patients with treatment resistant depression (TRD) that were also taking oral antidepressants.[7] Results were considered clinically significant, as demonstrated by a MADRS score change of 2 or more points. Two other trials did not demonstrate superiority of esketamine compared to placebo, in part due to a higher withdrawal rate in the high-dose group of esketamine patients, lower overall effect size than assumed in the protocol, and higher placebo response than anticipated.[7,8]
- Esketamine is only available through a Risk Evaluation and Mitigation Strategy (REMS) program, which includes receiving esketamine in a REMS certified healthcare setting and monitoring patients for two hours after administration. Esketamine has a boxed warning due to sedation, dissociation, abuse and misuse and increased suicidal thoughts and behaviors in pediatric patients and adolescents taking antidepressants. Dissociation was experienced in 41% of patients, nausea in 28%, dizziness in 29%, and sedation in 23%.[9]

Brexanolone (Zulresso)

- Intravenous (IV) brexanolone was more effective than placebo in reducing Hamilton Rating Scale for Depression (HAM-D) scores in women with post-partum depression (PPD) by a mean difference reduction ranging from -2.5 to -5.5 points ($p<0.05$).[10] Reduction in HAM-D scores are clinically meaningful for reductions of 3-7 points, indicating borderline clinically significant benefits of brexanolone compared to placebo. Results for the secondary outcome, Clinical Global Impression-Improvement (CGI-I) responders, was higher in patients randomized to brexanolone compared to placebo (number needed to treat [NNT] of 3-4).
- Brexanolone has a boxed warning for excessive sedation or sudden loss of consciousness requiring continuous pulse oximetry monitoring. Brexanolone is only available through a REMS program.[11]

Safety

- A high quality review from AHRQ found an increased risk of adverse events in the acute phase of treatment in older patients (65 years or older) treated with duloxetine and venlafaxine compared to placebo, with a number needed to harm (NNH) of 10 (high strength of evidence).[12] In the acute phase, withdrawals due to adverse events were increased with duloxetine and venlafaxine compared to placebo based on moderate evidence (relative risk [RR] 1.85; 95% CI, 1.05 to 3.27; NNH 17).[12] Vortioxetine was associated with less adverse events compared to duloxetine based on high strength of evidence (RR 0.80; 95% CI, 0.69 to 0.92; NNT 6).[12] High strength of evidence found decreased risk of any adverse events with vortioxetine compared to duloxetine in the acute phase of treatments (RR 0.80; 95% CI, 0.69 to 0.92; NNT 6).[12]

Recommendations:

- No changes to the preferred drug list (PDL) are recommended based on the review of clinical efficacy.
- Recommend prior authorization criteria for brexanolone and esketamine based on safety concerns.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy

- There is insufficient evidence of clinically significant differences in efficacy and safety between specific antidepressants or classes of antidepressants. Previous recommendations are to base antidepressant treatment selection on patient characteristics and cost.
- There were no policy changes based on efficacy or safety evidence presented in the last review.
- Anti-depressants are designated preferred or part of the voluntary PDL.

Background:

Antidepressants are most commonly used for MDD but have demonstrated efficacy in many other disorders, including: obsessive compulsive disorder, post-traumatic stress disorder, anxiety disorders and pain syndromes.[13] The therapeutic effect of antidepressants is to target serotonin, dopamine and norepinephrine levels.

Major depressive disorder is defined as a chronic disorder in patients experiencing depressed mood or diminished interest or pleasure in activities of daily living. Symptoms of depression are weight changes, changes in appetite and/or sleep, fatigue, feelings of worthlessness, inability to concentrate and feelings of death or suicide that last at least 2 weeks.[13] The cause of depression is usually a combination of internal, external and traumatic factors that coincide to precipitate MDD. The incidence of MDD has steadily increased with the lifetime incidence in the United States of 17%.[14] Females have almost twice the risk as males for the development of depression. MDD has been associated with the second leading cause of disability.

Antidepressants, in combination with cognitive behavioral therapy, are the main treatment modalities for the treatment of MDD.[13] Antidepressants are divided into first- and second-generation treatments. First-generation classes are tricyclics and monoamine oxidase inhibitors. Second generation antidepressants include SSRIs, SNRIs, atypicals, and serotonin modulators. The SSRIs increase serotonin and are recommended as first-line agents due to efficacy and tolerability. Commonly used second-line therapies include SNRIs and serotonin modulators.[13] There is no evidence of clinically meaningful differences in efficacy between the different antidepressants. Adverse effects, safety, comorbidities, drug interactions and cost are common determining characteristics in choosing antidepressant therapy.

Effectiveness of antidepressant treatment is based on symptom improvement, function, and quality of life. Treatment response is measured by a provider administered depression rating scale. Response is considered improvement of 50% or more but less than the threshold for remission. Remission is defined as a score less than or equal to a predefined "normal range" for that scale. Commonly used symptom scales are presented in **Table 1**.

Table 1. Depression Symptom Patient Assessment Tools

Assessment	Description	Remission Score	Clinically Meaningful Important Difference
Hamilton Rating Scale for Depression (HAM-D)[15,16]	17 items, each item has a range of 0-2	Less than or equal to 7	3 to 7

Montgomery-Asberg Depression Rating Scale (MADRS)[17]	10 items, clinician-rate scale, range of 0-60, higher scores indicate a higher severity of depression	MADRS total score of less than or equal to 12 for at least 3 of the last 4 weeks	1.6 to 1.9
Patient Health Questionnaire -9 item (PHQ-9)[18]	Nine items with a score of 0-27 based on a 4-point Likert score for each item	Less than 5	Treatment score of less than 9 and 50% improvement in symptoms
Clinical Global Impression-Improvement Score (CGI-I)[19]	7-point scale in which illness is documented as improved or worsened – higher scores represent worsening symptoms/functioning	Response defined as 1 (very much improved) or 2 (much improved)	Not described

Approximately 130,000 fee-for-service (FFS) patients had a diagnosis of MDD in the last year. Antidepressant therapy accounts for a large portion of the Oregon Health Authority (OHP) drug benefit budget. Medications in this class are preferred or on a voluntary PDL. In the last quarter, 64% of the antidepressant claims were for preferred therapies.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 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:

Depression
AHRQ- Adverse Effects of Pharmacological Treatments of Major Depression in Older Adults
A systematic review and meta-analysis was done by AHRQ to study the adverse effects of pharmacological treatments for MDD in adults, 65 years and older.[12] Classes of antidepressants included in the review are SSRIs, SNRIs and others (bupropion, mirtazapine, trazodone, vilazodone and vortioxetine). Specific outcomes of interest were: any adverse event, bleeding, blood pressure changes, cognitive measures and electrocardiogram changes, emergency department (ED) visits, falls, fractures, hospitalizations, mortality, seizures, suicidal thoughts/attempts, syndrome of inappropriate antidiuretic hormone secretion (SIADH) or hyponatremia, weight changes or withdrawals due to adverse events. Thirty-nine publications were included in the review, 37 were randomized controlled trials and two were observational studies. In general, evidence of clinical efficacy in patients 65 years and older is of low quality; however, SSRIs and bupropion XR are most commonly used.[12] Outcomes with moderate to high strength of evidence will be presented.

SSRIs versus Placebo or No Treatment

- There was moderate strength of evidence of no difference in adverse events in the acute phase between SSRIs (fluoxetine and escitalopram) and placebo or no treatment and the strength of evidence for all other outcome comparisons were of low or insufficient quality.[12]

SSRIs versus Tricyclic Antidepressants

- Three trials were identified comparing SSRIs versus TCAs; however, all findings were of low strength of evidence or insufficient findings.[12]

SSRIs versus SSRIs

- A comparison between sertraline and fluoxetine and a comparison between escitalopram and fluoxetine found moderate strength of evidence of no difference in the incidence of any adverse events in the acute phase.
- No difference in any adverse events or serious adverse events in the maintenance phase was found in a comparison between paroxetine and fluoxetine based on moderate evidence.[12]

SNRIs versus Placebo

- In the acute phase of treatment there was high strength of evidence of increased risk of adverse events with duloxetine and venlafaxine compared to placebo with a NNH of 10.[12]
- In the acute phase, withdrawals due to adverse events were increased with duloxetine and venlafaxine compared to placebo based on moderate evidence (RR 1.85; 95% CI, 1.05 to 3.27; NNH 17).[12]
- The risk of withdrawals due to adverse events was higher with duloxetine compared to placebo in the acute and continuation phase of treatment based on moderate strength of evidence with a NNH of 12 (RR 2.64; 95% CI, 1.21 to 5.73).[12]
- An increased risk of falls during the acute and maintenance phase was found with duloxetine versus placebo based on moderate strength of evidence (RR 1.69; 95% CI, 1.03 to 2.76; NNH 10).[12]
- There was moderate strength of evidence of no difference between duloxetine and placebo for the outcomes of ECG-QTc changes and serious adverse events in the acute and continuation phase.
- Serum sodium and body weight were reduced in the acute phase of MDD treatment in patients taking duloxetine compared to placebo (specific results not available).

SNRIs versus SSRIs

- There was no difference between the comparison of venlafaxine and citalopram for the outcomes of any adverse events, serious adverse events, or withdrawals due to adverse events in the continuation phase based on moderate evidence.[12]
- There was moderate strength of evidence of no difference between venlafaxine and fluoxetine for any adverse events in the acute phase.

Bupropion XR versus Placebo

- There was no evidence of differences between bupropion XR and placebo for the outcome of any adverse event based on moderate strength of evidence.[12]

Mirtazapine versus Paroxetine

- Moderate evidence found no difference in any adverse events in the acute treatment phase between mirtazapine and paroxetine.

Trazodone versus No Antidepressant Use

- All outcomes were of low strength of evidence.[12]

Vortioxetine

- There was no difference between vortioxetine compared to placebo for the outcomes of any adverse events and serious adverse events, in the acute phase, based on high and moderate strength of evidence, respectively.

- No difference in serious adverse events and withdrawals due to adverse events in the acute phase were found between vortioxetine versus duloxetine based on moderate evidence.
- High strength of evidence found decreased risk of any adverse events with vortioxetine compared to duloxetine in the acute phase of treatments (RR 0.80; 95% CI, 0.69 to 0.92; NNT 6).[12]

Limitations to the review are that none of the randomized controlled trials included in the review were specifically designed to study adverse events and, therefore, resulted in findings of low or insufficient evidence in some comparisons.

Cochrane – Antidepressants for Treating Depression in Dementia

A 2018 systematic review and meta-analysis done by Cochrane analyzed the efficacy and safety of antidepressant therapy in patients with a diagnosis of dementia and coexisting depression.[20] A literature search up until August of 2018 identified ten randomized controlled trials which were included in the qualitative synthesis. Eight trials were identified for the meta-analysis. The mean age of included participants was 80 years old and mean dementia severity was 19.65, as determined by the mean Mini Mental State Examination (MMSE) score, which is considered mild dementia.[20] Drug classes included in the study where tricyclic antidepressants (TCA), SSRIs, SSRI/SNRIs and one study evaluated a reversible monoamine oxidase inhibitor. All but two studies had unclear risk of bias. The primary outcome was the effect on depression (as determined by a response and remission based on rating scales). Other important outcomes include the number of patients with remission, effect on cognitive function, activities of daily living impact, adverse events and withdrawals.[20]

There was high quality evidence demonstrating no evidence of effectiveness for patients with dementia treated with antidepressants, compared to placebo, based on depression endpoint score ratings at 6 to 13 weeks (standard mean difference [SMD] -0.10 (95% CI, -0.26 to 0.06).[20] A subgroup analysis of only SSRIs found little or no difference of efficacy, based on score ratings, compared to placebo. The number of patients with remission at 6 to 12 weeks was found to be higher in patients with dementia treated with antidepressants compared to placebo, 217/1000 versus 415/1000 (OR 2.57; 95% CI, 1.44 to 4.59) based on moderate quality evidence.[20] Changes based on responder rates were considered low quality evidence and therefore not included. There was moderate quality evidence that antidepressant therapy was associated with more drop outs compared to placebo. Patients taking antidepressants were more likely to experience an adverse event compared to placebo based on moderate quality evidence. In summary, there is no strong evidence for the treatment of depression in patients with dementia.

Cochrane – Antidepressants for the Treatment of People with Co-occurring Depression and Alcohol Dependence

A 2018 Cochrane review was done to determine the efficacy and harms of antidepressant use in patients with alcohol dependence.[21] There were 33 randomized controlled trials that met inclusion criteria, 18 of the trials were conducted in an outpatient setting. Included patients were a mean age of 42 years and 68% were men. Trials ranged from 3 to 26 weeks and included placebo, psychotherapy and other medications (including other antidepressants).[21] Medications included in the review were amitriptyline, citalopram, desipramine, doxepin, escitalopram, fluoxetine, fluvoxamine, imipramine, mirtazapine, nefazodone, paroxetine, and venlafaxine. The primary outcome was the full remission of depression.

There was no difference found in the rate of full remission of depression in antidepressant versus placebo comparisons; however, there were only 4 included studies and there was a high degree of heterogeneity (I^2=66%).[21] There was moderate quality of evidence that the number of patients that were abstinent from alcohol were higher in the antidepressant group compared to placebo with RR of 1.71 (95% CI, 1.22 to 2.39; p=0.002).[21] In addition, the mean number of alcoholic drinks per day was lower in patient taking antidepressants compared to placebo by 1.13 drinks per drinking days (95% CI, 1.79 to 0.46).[21] All other studied outcomes were of very low or low quality evidence.

Limitations include a small number of include trials for comparison and one-third of studies were completed in countries outside the US. Overall, there is limited evidence of efficacy of antidepressants for the treatment of patients with co-occurring depression and alcohol dependence.

Anxiety

Cochrane – Pharmacotherapy for Social Anxiety Disorder (SAnD)

A 2017 Cochrane review evaluated treatments used for SAnD in adult patients.[4] Sixty-six trials met inclusion criteria for the review and approximately half were testing the efficacy of SSRIs. The average trial size was small with the average number of trial participants being 176, and all trials had durations of 24 weeks or less. The primary outcome was treatment response (assessed by CGI-I). Important secondary outcomes were SAnD symptom severity (assessed by the Liebowitz Social Anxiety Scale [LSAS]) and rate of relapse. The CGI-I ranges from 1-7 with higher numbers indicating very ill patients. A change of 1 represents (very much) improved and a change of 2 as (improved). The LSAS is a 24-item scale with higher scores representing a higher level of social anxiety (>95 indicating very severe social phobia).

Clinician rated LSAS total score demonstrated a reduction of anxiety symptoms by 11.91 points (95% CI −16.06 to −7.76; $p<0.05$) lower in the SNRI group compared to placebo, in patients with low to moderate social phobias. In patients that took SSRIs (paroxetine, fluvoxamine, sertraline, fluoxetine, and citalopram), there was moderate evidence of a reduced rate of relapse compared to placebo with a RR of 0.34 (95% CI, 0.22 to 0.5; $p<0.00001$).[4] In an overall comparison across all medication classes, there was evidence of higher efficacy with treatment compared to placebo; however, this analysis was associated with a high degree of heterogeneity ($I^2=69.7\%$).[4]

AHRQ – Anxiety in Children

An AHRQ review evaluated efficacy and harms of therapies for childhood anxiety disorders (e.g., panic disorder, social anxiety disorder, specific phobias, generalized anxiety disorder and separation anxiety).[3] A total of 206 studies compared psychotherapy, pharmacotherapy, or combination of treatments in children from the ages of 3 to 18 years. Primary anxiety symptoms were the primary outcome of interest.

In summary, SSRIs (fluoxetine, paroxetine, and sertraline) and SNRIs (atomoxetine, duloxetine and venlafaxine) improved primary anxiety symptoms compared to placebo based on moderate to high evidence.[3] SSRIs also demonstrated efficacy in improved remission rates, function, and clinical response compared to placebo (moderate to high strength of evidence). TCAs and benzodiazepines lacked conclusive evidence of benefit. Specific results for comparisons with moderate or high strength of evidence are presented in **Table 2**. Limitations to the data include small number of studies available for the analysis, small sample sizes, and imprecision in the data.

Table 2. Results for Evidence in the Treatment of Children with Anxiety[3]

Comparison	Outcome	Results*	Strength of Evidence
Drugs +/- Cognitive Behavioral Therapy [CBT] versus CBT			
Imipramine and CBT Vs. CBT	Primary anxiety/patient reported	SMD: -0.74 (95% CI, -1.26 to -0.23) *Imipramine and CBT reduced anxiety more than CBT alone*	Moderate
	Function	SMD: -1.27 (95% CI, -1.81 to -0.73) *Imipramine and CBT improved function more than CBT alone*	Moderate

CBT and sertraline Vs. CBT	Primary anxiety/clinician reported	SMD: -0.69 (95% CI, -0.93 to -0.45) *Sertraline and CBT reduced anxiety more than CBT alone*	Moderate
	Function	SMD: -0.47 (95% CI, -0.70 to -0.23) *Sertraline and CBT improved function more than CBT alone*	Moderate
Fluoxetine Vs. CBT	Primary anxiety/clinician reported	SMD: 0.78 (95% CI, 0.37 to 1.18) *Increased anxiety with fluoxetine*	Moderate
	Function	SMD: 0.54 (95% CI, 0.14 to 0.94) *Fluoxetine reduced function*	Moderate
Sertraline Vs. CBT	Remission	RR 1.51 (95% CI, 1.22 to 1.86) *Sertraline improved remission more than CBT*	Moderate
	Response	RR 1.47 (95% CI, 1.24 to 1.75) *Sertraline improved response more than CBT*	Moderate
CBT and sertraline Vs. Sertraline	Primary anxiety/clinician report	SMD: -0.46 (95% CI, -0.70 to -0.22) *CBT and sertraline reduced anxiety more than sertraline alone*	Moderate
	Function	SMD: -0.34 (95% CI, -0.58 to -0.10) *CBT and sertraline improved function more than sertraline alone*	Moderate
	Remission	RR 1.51 (95% CI, 1.22 to 1.87) *CBT and sertraline improved remission rates more than sertraline alone*	Moderate
	Response	RR 1.47 (95% CI, 1.24 to 1.75) *CBT and sertraline improved responses more than sertraline alone*	Moderate
Drugs versus Placebo			
SNRI Vs. Placebo	Primary anxiety/clinician report	SMD: -0.45 (95% CI, -0.81 to -0.10) *SNRIs reduced anxiety more than placebo*	High
SSRI Vs. Placebo	Primary anxiety/parent report	SMD: -0.61 (95% CI, -1.03 to -0.20) *SSRIs reduced anxiety more than placebo*	Moderate
	Primary anxiety/clinician report	SMD: -0.65 (95% CI, -1.10 to -0.21) *SSRIs reduced anxiety more than placebo*	Moderate
	Function	SMD: -0.59 (95% CI, -0.85 to -0.34) *SSRIs improved function more than placebo*	High
	Remission	RR 2.04 (95% CI, 1.37 to 3.04) *SSRIs improved remission rates more than placebo*	Moderate
	Response	RR 1.96 (95% CI, 1.60 to 2.40) *SSRIs improved response rates more than placebo*	Moderate

Key: * SMD cutoffs of 0.20, 0.50, and 0.80 are considered to represent small, moderate, and large effect, respectively.

Abbreviations: CBT = cognitive behavioral therapy, CI = confidence interval; SMD = standard mean difference; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor

Cochrane – Antidepressants versus Placebo for Panic Disorder in Adults

The efficacy and harms of antidepressants for the treatment of panic disorder in adults was the topic of a recent Cochrane systematic review.[22] Forty-one randomized, placebo-controlled trials were included with study durations of 8 to 28 weeks. Classes of drugs that were included in the review were: TCAs (17 studies), SSRIs (22 studies), SNRIs (4 studies), MAOIs (1 study), norepinephrine reuptake inhibitor (NRI) (1 study – reboxetine, which is not available in the US). Two studies had active treatment comparisons (nefazodone and ritanserin). Most studies had an unclear risk of selection and performance bias.

There was moderate quality evidence demonstrating less dropouts in patients taking antidepressants compared to placebo with a mean difference of 38 fewer dropout per 1000 patients (RR 0.88; 95% CI, 0.81 to 0.97; number needed to benefit [NNTB] 27).[22] The benefit was driven by TCAs, as there was no difference from placebo for SSRIs and SNRIs. Risk associated with failure to obtain remission was lower with antidepressant treatment compared to placebo based on moderate evidence (RR 0.83; 95% CI, 0.78 to 0.88), and a mean difference of 101 patients per 1000 treated fewer patients failed to remit in the antidepressant group.[22] There was an increased risk of dropouts due to adverse events in the antidepressant group compared to placebo with a RR of 1.49 (95% CI, 1.25 to 1.78), based on moderate evidence.[22] This was most common with TCAs and SSRIs.

Limitations to this review include unclear risk of bias in some domains and insufficient long-term data. Overall, there is not robust evidence to support the treatment of panic disorder in adults with antidepressants.

Wang, et al. – Comparative Effectiveness and Safety of Cognitive Behavioral Therapy and Pharmacotherapy for Childhood Anxiety Disorders

A recent good quality systematic review and meta-analysis included 7719 children and adolescents (mean age of 9 and 56% female) with a diagnosis of panic disorder (31%), social anxiety disorder (71%), specific phobias, generalized anxiety disorder (63%) or separation anxiety (61%) that were receiving cognitive behavioral therapy (CBT), pharmacotherapy or both.[2] Patients who were using pharmacotherapy were on SSRIs, SNRIs, tricyclic antidepressants (TCAs), and benzodiazepines. Most studies were up to 12 weeks in duration with the longest study lasting 32 weeks. The overall risk of bias was considered moderate to high due to lack of blinding of patients, providers, and outcome assessors, in addition to an unclear risk of conflicts of interest. Determination of publication bias, related to pharmacotherapy, was not done due to lack of studies. The primary outcome of the review was the occurrence of primary anxiety symptoms (as measured by a standardized measure of child anxiety symptoms), clinical remission, treatment response and adverse events.[2]

There was moderate quality of evidence that SSRIs were more effective at reducing anxiety symptoms compared to placebo, as reported by parents (SMD -0.61; 95% CI, -1.03 to -0.20) and clinicians (SMD -0.65: 95% CI, -1.10 to -0.21).[2] There was high heterogeneity with both findings, ranging from 55% to 73%. SSRIs were also associated with higher remission rates compared to placebo (RR 2.04; 95% CI, 1.37 to 3.04) and response (RR 1.96; 95% CI, 1.60 to 2.40), both based on moderate quality of evidence.[2] The efficacy of SNRIs on primary anxiety symptom reduction, as reported by clinicians, was higher than placebo based on high quality of evidence and a standard mean difference of -0.45 (95% CI, -0.81 to -0.10).[2] Active treatment was more commonly associated with adverse events but none were considered serious.

CBT was more effective than wait listing/no treatment in reducing primary anxiety symptoms based on child, parent and clinician assessments, SMD -0.77, -0.88 and -1.38, respectively (moderate quality evidence).[2] Clinician-assessed treatment response was also improved based on moderate quality evidence (RR 4.72; 95% CI, 2.39 to 9.32).[2] All estimates had a high degree of heterogeneity. Moderate quality evidence found the combination therapy of imipramine and CBT, compared to CBT alone, reduced primary anxiety symptoms based on child assessment, SMD of -0.74 (95% CI, -1.26 to -0.23).[2] Sertraline combined with CBT reduced primary anxiety symptoms (SMD 0.69; 95% CI, -0.93 to -0.45), improved treatment response (RR 1.35; 95% CI, 1.15 to 1.58), and remission (RR 1.51; 95% CI, 1.22 to 1.86) when compared to CBT alone based on clinician assessment.[2] In a comparison of sertraline to CBT, there was no difference in the reduction of primary anxiety

symptoms. There was moderate quality evidence that CBT was more effective than fluoxetine at reducing primary anxiety symptoms based on clinician assessment (SMD -0.78; 95% CI, -1.18 to -0.37).[2]

Posttraumatic Stress Disorder

AHRQ- Psychological and Pharmacological Treatments for Adults with Posttraumatic Stress Disorder

A systematic review and meta-analysis was done by AHRQ to evaluate the efficacy and harms of treatments for PTSD.[5] This 2018 report updates a previous 2013 version. The report analyzes the psychological as well as pharmacotherapy recommendations; however, the focus of this summary will be on the evidence for medications which included the following classes: SSRIs, SNRIs, TCAs, and other second-generation antidepressants (bupropion, mirtazapine, nefazodone, and trazodone). Paroxetine and sertraline are the only therapies approved for the treatment of PTSD; however, the other therapies are often used off-label for the treatment of PTSD. Patients 18 years old and older with PTSD (diagnosed by any DSM criteria) were included.[5] The primary outcome was the reduction in PTSD symptoms.

There was moderate quality of evidence that treatment with fluoxetine, paroxetine and venlafaxine were more effective than placebo (**Table 3**).[5] All studies of fluoxetine, paroxetine and venlafaxine demonstrated medium risk of bias. Overall, SSRIs were associated with a reduction in clinician administered PTSD symptom scores, with a SMD of -0.30 (95% CI, -0.40 to -0.20; p=0.041).[5] Depression symptoms were reduced with SSRIs compared to placebo in patients with PTSD by a SMD of -0.24 (95% CI, -0.38 to -0.11; p<0.001).[5] Two trials provided direct evidence comparisons; venlafaxine extended release (ER) versus sertraline and paroxetine + placebo versus desipramine + placebo. Both trials found similar decreases in PTSD symptoms; however, comparisons were considered insufficient or low strength of evidence. A head to head comparison of venlafaxine ER to sertraline found moderate strength of evidence of no difference for changes in depression symptoms.

Table 3. Outcomes for Pharmacological Treatment used in PTSD with Moderate to High Strength of Evidence (placebo comparisons)[5]

Treatment	Outcome	Result	Interpretation	Strength of Evidence
Fluoxetine	PTSD symptoms	SMD -0.28 (95% CI, -0.42 to -0.14)	Fluoxetine reduced PTSD symptoms	Moderate
Paroxetine	PTSD symptoms	SMD -0.44 to -0.56 (CI not provided)	Paroxetine reduced PTSD symptoms	Moderate
	PTSD symptom remission	RD 0.13 to 0.19 (CI not provided)	Paroxetine was associated with greater PTSD symptom remission	Moderate
	Depression symptoms	SMD -0.60 to -0.34 (CI not provided)	Paroxetine reduced depression symptoms	Moderate
Venlafaxine	PTSD symptoms	SMD -0.35 to -0.26 (CI not provided)	Venlafaxine reduced PTSD symptoms	Moderate
	PTSD symptom remission	RD of 0.12 to 0.15 (CI not provided)	Venlafaxine was associated with greater PTSD symptom remission	Moderate
	Depression symptoms	SMD -2.6 to -1.6 (CI not provided)	Venlafaxine was associated with reduced depression symptoms	Moderate
Abbreviations: CI = confidence interval; PTSD =posttraumatic stress disorder; RD =risk difference; SMD = standardized mean difference				

Direct comparative effectiveness evidence was insufficient for most pharmacotherapy comparisons for PTSD and for commonly used treatments such as escitalopram, fluvoxamine, desvenlafaxine, duloxetine, TCAs and other second-generation antidepressants.

After review, 22 systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:

NICE – Depression in Adults: Recognition and Management

A 2009 review that was updated in April 2018 provided guidance for adults who present with depression as the primary diagnosis.[16] If antidepressants are indicated, a choice should be made based on adverse events, drug interactions, patient comorbidities and perception and tolerability of previous treatments. Recommendations:

- Generic SSRIs are recommended first-line based on efficacy and tolerability.
    - SSRIs have an increased risk of bleeding and caution is advised in older patients or in patients taking other medications that are known to damage the mucosa of the gastrointestinal tract or interfere with clotting.
    - Drug interactions are most common with fluoxetine, fluvoxamine, and paroxetine.
    - Paroxetine is associated with a high risk of discontinuation.
- For patients at increased risk of suicide:
    - Venlafaxine is associated with a higher risk of death due to overdose than other equally effective antidepressants used for routine use in primary care.
    - TCAs are associated with the greatest risk of overdose.
- The following considerations are warranted with antidepressant use other than SSRIs
    - Higher discontinuation rates with TCAs
    - Some antidepressants may require monitoring, have specific cautions or contraindications which need to be considered with each individual patient.
- If symptoms have not improved in 3-4 weeks of antidepressant therapy consider increasing the antidepressant dose or switching to another antidepressant.

NICE – Post-traumatic Stress Disorder

NICE updated their guidance on post-traumatic stress disorder in 2018. Medication therapy is not recommended for prevention of PTSD.[6] If medication is appropriate for treatment, venlafaxine or a SSRI (e.g., sertraline) is recommended for adult patients. Treatment effectiveness should be assessed frequently and monitored for adverse reactions. Antipsychotics, such as risperidone, should be considered only with the following qualifying factors: presence of disabling symptoms and behaviors (e.g., severe hyperarousal or psychotic symptoms) and when symptoms have not responded to other drug or psychological treatments.

NICE – Depression in Children and Young People: Identification and Management

The treatment of depression in children and young people was the focus of a September 2017 update.[1] In patients with mild depression, antidepressant therapy is not recommended for initial treatment in children and young people. All antidepressant treatment should be offered in conjunction with psychotherapy and follow an assessment and diagnosis by a child and adolescent psychiatrist. In individuals with moderate to severe depression who continue to have symptoms despite the care of a multidisciplinary team, fluoxetine should be offered if patients are 12-18 years old. In younger children, ages 5 to 11, fluoxetine could be cautiously considered if they are unresponsive to psychological therapy (minimum of 4 sessions), although evidence is limited. Guidance for the use of antidepressants in children and young people is outlined in **Table 4**.[1] Venlafaxine, paroxetine and TCAs should not be used in children and young people for the treatment of depression.

Table 4. Recommendations for Medication Use in Children and Young Persons[1]

First-line Therapy - Fluoxetine
• Starting fluoxetine dose should be 10 mg daily • Fluoxetine dose can be increased to 20 mg daily after 1 week if clinically indicated • Medication should be continued for at least 6 months after remission
Second-line Therapies
• Sertraline or citalopram are the recommended second-line therapies • Medication should be continued for at least 6 months after remission • Starting dose should be half the adult dose • Dose can be titrated over the next 2 to 4 weeks up to the adult dose, if clinically indicated

US Preventative Services Task Force – Interventions to Prevent Perinatal Depression

A systematic review and meta-analysis was completed in 2019 to determine the benefits and harms of interventions offered in primary care to prevent perinatal depression (major or minor depressive episode during pregnancy or up to 1 year after childbirth).[23] Randomized and non-randomized controlled trials were included. Behavior-based interventions, antidepressants, and dietary supplements were studied for prevention in perinatal depression in pregnant and postpartum women or those at increased risk of perinatal depression. There was insufficient evidence to determine the benefits or harms of antidepressants in this population.

After review, four guidelines were excluded due to poor quality.[24–27]

New Formulations or Indications:

None identified.

New FDA Safety Alerts:

None identified.

Randomized Controlled Trials:

A total of 155 citations were manually reviewed from the initial literature search. After further review, 154 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining trial is summarized in the table below. The full abstract is included in **Appendix 2**.

Table 5. Description of Randomized Comparative Clinical Trials

Study	Comparison	Population	Primary Outcome	Results
Jacobsen, et al[28] RCT, DB, MC	Vortioxetine Vs. Escitalopram (8 weeks)	Adults (40% male) with well-treated MDD experiencing treatment-emergent sexual dysfunction (n=447)	Change from baseline in the CSFQ-14 total score after 8 weeks	Vortioxetine: 8.8 Escitalopram: 6.6 MD: 2.2 (CI not provided) P = 0.013 *Vortioxetine improved sexual dysfunction scores more than escitalopram*
Key: CSFQ-14 – 14 item scale with 36 items with higher scores indicating higher sexual frequency[29] Abbreviations: CSFQ-14 = Changes in Sexual Functioning Questionnaire Short Form; DB =double-blind; RCT-=randomized controlled trial				

NEW DRUG EVALUATION: Esketamine (Spravato™)

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:

Esketamine is a Schedule III nasal spray which is a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist indicated for use in conjunction with oral antidepressants for the treatment of TRD in adults.[9] Esketamine should be administered under the supervision of a medical provider and is made available only through a restricted program called the Spravato REMS. The dose of esketamine ranges from 56-84 mg and is given twice weekly during the induction phase and once weekly during the maintenance phase (**Table 6**). Patient should be monitored for 2 hours after administration. Baseline blood pressure monitoring and blood pressure reassessment at 40 minutes post-dose, and subsequently if warranted, is recommended.[9]

Table. 6. Esketamine Intranasal Dosing Recommendations[9]

Phase	Dose
Induction Phase – weeks 1-4 Twice weekly dosing	56 mg for initial dose; subsequent doses are 56-84 mg. At the end of the induction phase, the maintenance phase dose should be continuation of the initial dose.
Maintenance Phase – weeks 5-8	56 or 84 mg once weekly
Maintenance Phase – week 9 and thereafter	56 or 84 mg once weekly or once every other week (i.e., every 2 weeks)
* Each device contains 28 mg of esketamine in two sprays; 2 devices for the 56 mg dose and 3 devices for the 84 mg dose	

Five, phase 3, randomized, placebo-controlled trials (TRANSFORM-1, TRANSFORM-2, TRANSFORM-3, SUSTAIN-1, SUTSTAIN-2) were used to determine the clinically efficacy and safety of esketamine in adult patients with TRD. TRANSFORM-2 and SUSTAIN-1 are the only published study so the efficacy and safety results of the other trials will be based on data from prescribing information and the esketamine dossier.[7,8]

TRANSFORM-2 included patients (n=223), mean age of 47 years, with MDD (mean MADRS score of 37) who had not responded adequately to at least two different antidepressants appropriately titrated and treatment of adequate duration in the current depressive episode (**Table 9**).[7] All patients received open-label oral antidepressant therapy, 32% SSRI (escitalopram, sertraline) and SNRI in 68% (duloxetine, extended-release venlafaxine). The primary outcome measure was change from baseline MADRS total score at the end of week 4. Important secondary endpoints were the number of responders (MADRS score decrease of 50% or more), number of patients obtaining remission (MADRS score of equal to or less than 12) and change in CGI-S at week 4. Esketamine decreased MADRS scores more than placebo, -21.4 and -17.0 (MD -4.0; 95% CI, -7.3 to -0.64; P=0.020) at day 28, which was clinically and statistically significant.[7] Response and remission rates (based on MADRS) and CGI-S scores were not statistically different.

A randomized, withdrawal study was conducted to determine the efficacy of esketamine compared to placebo in a relapse prevention trial (SUSTAIN-1).[30] Patients were classified as direct-entry patients (which participated in screening, induction, optimization, maintenance and follow-up phases), and transfer-entry patients (responders from previous esketamine studies) who were in the optimization, maintenance and follow-up phases only. One-hundred seventy-six patients that were stable remitters during the maintenance phase were randomized to either 56-84 mg esketamine + oral antidepressant or to placebo + oral antidepressant for the primary analysis of relapse rates. A secondary endpoint was an analysis of relapse rates in patients who had a stable response in the optimization phase (n=121). Esketamine + oral antidepressant was associated with a relapse rate of 26.7% versus 45.3% in the placebo + antidepressant group (p=0.003/NNT 6).[30] For the secondary analysis of the number of patients with a stable response that experienced a relapse, 25.8% in the esketamine + antidepressant group and 57.6% in the placebo + antidepressant group had a relapse (p<0.001/NNT 3).[30] The mean exposure time was 17.7 weeks for both analyses.

TRANSFORM-1 was a randomized, double-blind, multi-center trial in 346 patients. Patients were randomized to fixed dose esketamine 56 or 84 mg or placebo with both groups also taking an oral antidepressant. After 4 weeks of treatment, mean change in MADRS scores were: -19.0 for esketamine 56 mg, -18.8 for esketamine 84 mg and -14.8 for the placebo group. Changes were not found to be statistically significant (p=0.088). A similarly designed trial (TRANSFORM-3) was done in elderly patients, 65 years and older (n=137). At four weeks, a mean change from placebo + antidepressant of -3.7 points on the MADRS scale was demonstrated, which was not statistically significant (p=0.059).

Limitations to the studies include small sample size and short treatment duration all efficacy studies. There is low external validity due to extensive exclusion criteria and the allowance of only four different oral antidepressants. The relapse prevention study biased trial results towards patients that were esketamine responders or remitters to treatment during the optimization phase. This study also increased the number of patients experiencing relapses after an interim analysis did not show superiority of esketamine + oral antidepressant compared to placebo + oral antidepressant. Patients were also started on a new oral antidepressant, in both groups, which could influence efficacy results in both groups.

Clinical Safety:
Common adverse events associated with esketamine are presented in **Table 7**.[9] Adverse events experienced in patients taking esketamine, with an incidence of at least 5% or more, and twice placebo rates in patients also taking antidepressants, where dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, increased blood pressure, vomiting and feeling drunk.[9] The most common psychological effects were dissociation, perceptual changes, derealization and depersonalization given esketamine. Precautions include cognitive impairment, embryo-fetal toxicity and increased blood pressure. See prescribing information for all warnings and precautions.

Table 7. Some of the Adverse Reactions Reported in Greater than or equal to 2% of Esketamine Treated Patients and More than Placebo[9]

Adverse Reaction	Esketamine + oral antidepressant (N=346)	Placebo + oral antidepressant (N=222)
Dissociation	41%	9%
Dizziness	29%	8%
Nausea	28%	9%
Sedation	23%	9%
Vertigo	23%	3%
Anxiety	13%	6%
Increased blood pressure	10%	3%
Vomiting	9%	2%
Feeling Drunk	5%	0.5%
Feeling abnormal	3%	0%

Esketamine REMS Program Requirements[9]

- Pharmacies must be certified in the REMS in order to dispense to certified healthcare setting.
- Healthcare setting must be certified in the REMS in order to treat patients with esketamine nasal spray.
- Patient must be enrolled in the esketamine REMs to receive treatment.
- Provider must supervise administration, post-administration monitoring and provide patient education about potential serious outcomes associated with sedation and dissociation.
- Patients must be observed as least 2 hours administration for resolution of dissociation effects and sedation.
- Blood pressure should also be monitored for transient blood pressure increases lasting around 4 hours. Baseline blood pressure prior to administration and blood pressure 40 minutes post-dose should be taken to monitor for transient blood pressure increases.

A 52-week safety study (SUSTAIN-2) was done in 802 patients with treatment resistant depression, mean age of 52 years, and 63% females.[8] Patients were entered into a 4-week induction phase followed by a 48 day optimization and maintenance phase. The primary outcome was to evaluate safety with the change in MADRS score being a secondary outcome. Approximately 9.5% of patients in the esketamine + antidepressant group discontinued due to adverse events by the end of the maintenance phase and 4.1% of patients in the placebo + antidepressant group. Concerning adverse events of acute hypertension, severe dissociation and severe sedation were seen in 2.3%, 1.4% and 0.5% of patients, respectively during the induction phase and 3.0%, 0.7% and 0.2% of patients, respectively during the optimization/maintenance phase.[8]

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Remission of depressive symptoms
2) Relapse of depressive episode
3) Symptom reduction (as determined by a validated scale)
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Change in MADRS score at day 28

Table 8. Pharmacology and Pharmacokinetic Properties of Esketamine.

Parameter	
Mechanism of Action	non-competitive N-methyl D-aspartate (NMDA) receptor antagonist with the exact antidepressant mechanism unknown
Nasal Bioavailability	48%
Distribution and Protein Binding	709 Liters; protein binding 43-45%
Elimination	<1% unchanged in the urine
Half-Life	7-12 hours
Metabolism	P450 (CYP) enzymes CYP2B6 and CYP3A4 and to a lesser extent CYP2C9 and CYP2C19

Table 9. Esketamine 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. Popova, et al[7] Phase 3, DB, PC, RCT	1. Esketamine nasal spray (56 -84 mg) + oral antidepressant twice weekly† (E) 2. Placebo nasal spray + oral antidepressant twice weekly† (P) 28 days	Demographics: Age: 45 years Male: 38% SNRI at baseline: 68% Average MADRS score: 37 Key Inclusion Criteria: - 18-64 years - single episode (greater than or equal to 2 years) or recurrent major depressive disorder without psychotic features - score of 34 or greater on the IDS-C - diagnosis of treatment resistant depression* Key Exclusion Criteria: - current or recent homicidal suicidal ideation/intent or suicidal behavior within the past 6 months - psychotic disorder, MDD with psychotic features, bipolar or related disorders, antisocial, histrionic or narcissistic personality disorder, OCD or intellectual disability - seizures, uncontrolled hypertension - substance use disorder	mITT: 1. 116 2. 111 PP: 1. 98 2. 99 Attrition: 1. 16% 2. 11%	Change in baseline of MADRS score at day 28: E: -21.4 points P: -17.0 points E vs. P LSMD -4.0 (95% CI, -7.31 to -0.64) p-value: 0.020 Secondary Endpoints: MADRS clinical response: E: 9 (7.9%) P: 5 (4.6%) p-value: 0.321	 NA NS	Discontinuations due to Adverse Events: E: 8 (7.0%) P: 1 (0.9%) Dissociation: E: 30 (26%) P: 4 (3.7%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) Randomized 1:1, computer generated. Baseline characteristics similar except for a higher number of females in the esketamine group compared to placebo, 66% versus 58%. Performance Bias: (low) Double-blind design, investigators, patients, study team, site staff, principle investigator were all blinded to treatment allocation. Identical packaging was used to maintain blinding and well as flavoring agent. Detection Bias: (low) Data analysis was blinded and MADRS assessments were done by independent (remote) blinded evaluators. Attrition Bias: (high) attrition was high both groups. Results analyzed via a mITT analysis. Reporting Bias: (high) study was funded by manufacturer and response and remission analysis was post-hoc. **Applicability**: Patient: Applies to patients with severe depression taking oral antidepressants that do not have other personality disorders (low external validity) and have had an inadequate response to at least two antidepressants. Studies in patients 65 and older found no benefit compared to placebo. Intervention: Appropriate dose based on pharmacokinetic studies. Comparator: Placebo appropriate for efficacy studies. Active treatment comparison would be helpful. Outcomes: MADRS is a validated tool to assess therapeutic efficacy of antidepressants. Setting: Thirty-nine centers (26% in US study sites).

1. Daly, et al[30] SUSTAIN-1 Phase 3, DB, PC, MC, RCT	1. Esketamine nasal spray (56 -84 mg) + oral antidepressant twice weekly (E) 2. Placebo nasal spray + oral antidepressant twice weekly† (P) Mean exposure: 17.7 weeks - 4-week screening and prospective observation phase (direct-entry patients only∝) - 4-week open-label induction phase (direct-entry patients only∝) - 12-week optimization phase (direct-entry or transfer-entry patients∝) - event driven maintenance phase - 2-week post-treatment follow-up	Demographics: Age: 46.3 years Female: 66.3% Average MADRS score: 38.5 Key Inclusion Criteria: - 18-64 years - Achieved clinical treatment response‡ to esketamine nasal spray in 1 of 2 previous trials - single episode (greater than or equal to 2 years) or recurrent major depressive disorder without psychotic features - score of 34 or greater on the IDS-C - diagnosis of treatment resistant depression* - MADRS score of 28 or higher Key Exclusion Criteria: - suicidal behavior within the past year - current or recent homicidal or suicidal ideation or intent - MDD with psychotic features, personality disorder, OCD or intellectual disability - seizures, uncontrolled hypertension - moderate to severe substance or alcohol use disorder within the last 6 months - history of ketamine use disorder	mITT (remission): 1. 90 2. 86 PP (remission): 1. 82 2. 77 Attrition (remission): 1. 9% 2. 10% mITT (stable response): 1. 62 2. 59 PP (stable response): 1. 57 2. 56 Attrition (stable response): 1. 8% 2. 5%	Relapse in Patient who were in Stable Remission: E: 24 (26.7%) P: 39 (45.3%) HR 0.49 (95%CI, 0.29 to 0.84) p-value: 0.003 Secondary Endpoints: Relapse in patients who had a Stable Response: E: 16 (25.8%) P: 34 (57.6%) HR 0.30 (95% CI, 0.16 to 0.55) p-value: <0.001	19/6 32/3	Dysgeusia: E: 41 (27%) P: 10 (6.9%) Dissociation: E: 35 (23%) P: 0 (0%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) Randomized based on if obtained stable remission or response by a computer-generated schedule. Performance Bias: (unclear) Double-blind design but details not provided. Identical packaging was used to maintain blinding. Detection Bias: (low) Data analysis was blinded and MADRS assessments were done by independent (remote) blinded evaluators. Attrition Bias: (low) attrition was low both groups. Results analyzed via a mITT analysis. Reporting Bias: (high) study was funded by manufacturer. **Applicability**: Patient: Applies to patients with treatment resistant depression taking oral antidepressants that do not have other personality disorders (low external validity) and had a positive response to esketamine treatment. Intervention: Appropriate dose based on pharmacokinetic studies. Comparator: Placebo, with oral antidepressant, appropriate for efficacy studies. Active treatment comparison would be helpful. Outcomes: Remission is an appropriate outcome. Setting: Centers in US, Europe and Canada.

Key: * Treatment-resistant depression: nonresponse to an adequate trial (dosage, duration, and adherence) of at least 2 antidepressants in the current episode (of which one was observed prospectively); † Newly initiated open-label oral antidepressant (escitalopram, sertraline, duloxetine or venlafaxine) administered daily, ‡ Clinical response was defined as a ≥50% reduction in MADRS score by day 2 maintained to the end of the double-blind treatment phase with one excursion (i.e., a ≥25% reduction relative to baseline MADRS was allowed on day 8, 15 or 22); ∝ Direct-entry patients were underwent the screening and inductions phase and all patients who had a clinical response‡ at the end of the induction phase went into the optimization, maintenance and follow-up phases

Abbreviations: ARR = absolute risk reduction; CGI = Clinical Global Impression-Improvement response; CI = confidence interval; IDS-C =Inventory of Depressive Symptomatology- Clinician Rating; LSMD = least squares mean difference; MADRS = Montgomery-Asberg Depression Rating Scale; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; OCD = obsessive compulsive disorder; PC = placebo-controlled; PP = per protocol; PPD = post-partum depression; SNRI = serotonin norepinephrine reuptake inhibitor

NEW DRUG EVALUATION: Brexanolone (Zulresso)

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:
Brexanolone is a GABA $_A$ receptor positive modulator (similar to progesterone, which is reduced after pregnancy) indicated for the treatment of moderate to severe PDD in adults.[11] Brexanolone is administered by IV and titrated from a starting dose of 30 mcg/kg/hour up to a maximum dose of 90 mcg/kg/hour and back down again, over 60 hours. FDA approval was based on 2, double-blind, randomized, identical phase 3 trials (n= 226). Women were eligible if they were 18-45 years and had a HAM-D score indicating severe to very severe depression. In the first study, the mean age was 27 years, 25% had current antidepressant use at baseline, and the average HAM-D score was 29.[11] In the second study, the mean age was 28 with antidepressant use in 18% at baseline and average HAM-D score of 23.[10] Patients were followed for a total of 30 days. The mean time of brexanolone administration was approximately 4 months after delivery. The primary endpoint was change in the 17-item HAM-D total score from baseline at 60 hours. An important secondary endpoint was CGI-I response at 60 hours, which was a change of 1-2 points on the CGI-I scale.

In the first study, patients were randomized 1:1:1 to brexanolone 60 mcg/kg/hr (BX60), brexanolone 90 mcg/kg/hour (BX90) or placebo infusion over 60 hours (**Table 12**).[10] The changes in HAM-D scores were statistically significant compared to placebo for the BX60 and BX90 dose, -5.5 and -3.7 points, respectively.[10] Changes in the CGI-I response compared to placebo were statistically significant with 26-31% of patients responding to treatment (NNT of 4 for both doses). In the second study, BX90 decreased HAM-D scores by -2.5 points (p=0.016) more than placebo, which is not considered a clinically meaningful change. The change in CGI-I response was greater than placebo by 39% (NNT of 3).[10]

Trial limitations include small sample sizes and short-term durations. Adverse events associated with brexanolone may have alerted investigators to treatment randomization, potentially causing investigator bias. Background antidepressants were allowed and used in approximately 30% of the study participants.

Clinical Safety:
Common adverse reactions which occurred at least 5% more often and at least twice the rate of placebo were sedation/somnolence, dry mouth, loss of consciousness and flushing/hot flush (**Table 10**).[11] Dose interruption or reduction due to sedation and somnolence occurred more frequently in patients receiving brexanolone compared to placebo, 5% versus 0%, respectively. Loss of consciousness also occurred in 4% of brexanolone treated patients compared to none in the placebo group. Sedative effects should be evaluated every 2 hours during the infusion. Consequently, there is a boxed warning, due to risk of excessive sedation or sudden loss of consciousness. For these reasons, while administering brexanolone patients should have continuous pulse oximetry monitoring and brexanolone is only available through a REMS program.

Requirement of the REMS program are:

- healthcare facilities must be enrolled in the program and brexanolone must only be administered to patients who are enrolled in the program,
- pharmacies must be certified with the program and must only dispense brexanolone to healthcare facilities who are certified in the brexanolone REMS,
- patients must be enrolled in the brexanolone REMS prior to administration, and
- wholesalers and distributors must be registered with the program and must only distribute to certified healthcare facilities and pharmacies.[11]

Breast feeding was not permitted during the trials. It is estimated that 2% or less of the maternal dose would be excreted into breast milk.

Table 10. Adverse Reactions Reported in Greater than or equal to 2% of Brexanolone Treated Patients and More than Placebo[11]

Adverse Reaction	Placebo	Brexanolone 60 mcg/kg/hour	Brexanolone 90 mcg/kg/hour
Sedation, somnolence	6%	21%	13%
Dizziness, presyncope, vertigo	7%	13%	12%
Dry mouth	1%	11%	3%
Loss of consciousness	0	5%	3%
Flushing, hot flush	0	5%	2%
Diarrhea	1%	3%	2%
Oropharyngeal pain	0	3%	2%
Tachycardia	0	0	3%
Dyspepsia	0	0	2%

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Remission of depressive symptoms
2) Relapse of depressive episode
3) Symptom reduction (as determined by a validated scale)
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

2) Change in 17-item HAM-D total score at 60 hours

Table 11. Pharmacology and Pharmacokinetic Properties of Brexanolone

Parameter	
Mechanism of Action	Thought to be due to its positive allosteric modulation of $GABA_A$ receptors
Oral bioavailability	NA
Distribution and Protein Binding	3 Liters/kg >99%
Elimination	47% in the feces and 42% in the urine
Half-Life	9 hours
Metabolism	Non-CYP based pathways via three main routes (keto-reduction, glucuronidation, and sulfation.

Abbreviations: Not applicable

Table 12. Brexanolone 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. Meltzer-Brody, et al[10] Phase 3, DB, PC, RCT	1. Brexanolone 90 mcg/kg per hour IV over 60 hours (BX90) 2. Brexanolone 60 mcg/kg per hour IV over 60 hours (BX60) 3. Placebo IV over 60 hours (P)	Demographics: Age: 27 years Depression: 43% Previous PPD: 36% Baseline antidepressant use: 25% Average HAM-D score: 29 Key Inclusion Criteria: - 18-45 years - 6 months or less post-partum at screening with PPD - qualifying 17-item HAM-D score (greater than or equal to 26) Key Exclusion Criteria: - renal failure requiring dialysis - anemia - allergy to allopregnanolone or progesterone - history of schizophrenia, bipolar disorder, schizoaffective disorder	mITT: 1. 41 2. 38 3. 43 PP: 1. 36 2. 35 3. 42 Attrition: 1. 9% 2. 19% 3. 7%	Change in 17-item HAM-D total score at 60 hours: BX90: -17.7 points BX 60: -19.5 points P: -14.0 points BX90 vs. P LSMD -3.7 (95% CI, -6.9 to -0.5) p-value: 0.0252 BX 60 vs. P LSMD -5.5 (95% CI, -8.8 to -2.2) p-value: 0.0013 Secondary Endpoints: CGI-I response: BX90: 32 (82%) BX60: 31 (87%) P: 24 (56%) BX90 vs. P: OR 4.0 (95% CI, 1.4 to 11.6) p-value: 0.0095 BX60 vs. P: OR 4.0 (95% CI, 1.3 to 11.7) p-value: 0.0131	NA 26/4 31/4	Discontinuations due to Adverse Events: BX90: 0 BX60: 1 (3%) P: 1 (2%) Severe Adverse Event: BX90: 0 BX60: 1 (3%) P: 0	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) Randomized 1:1:1, 25% manually and 75% electronically. Baseline characteristics were well matched except for there was a lower number of patients with an anxiety diagnosis in the placebo group compared to brexanolone groups, 33%, 43%, and 47%, respectively. Performance Bias: (unclear) Double-blind design, investigators, patients, study team, site staff, principle investigator were all blinded to treatment allocation. Infusion rates were matched to avoid unblinding. Detection Bias: (unclear) Scores were determined by masked site investigators and approximately 50% were recorded. However, adverse events associated with brexanolone could potentially alert providers to randomization. Scoring may be subject to investigator bias. Attrition Bias: (high) attrition was high in the 60 mcg brexanolone group, with differences greater than 10% versus comparators. Results analyzed via a mITT analysis. Reporting Bias: (high) study was funded by manufacturer **Applicability**: Patient: Applies to women with severe depression, with or without current antidepressant use. Intervention: Appropriate dose based on pharmacokinetic studies Comparator: Placebo appropriate for efficacy studies. Active treatment comparison would be helpful. Outcomes: HAM-D is a validated tool to assess therapeutic efficacy of antidepressants. Setting: Thirty centers in the USA.
2. Meltzer-Brody, et al[10] Phase 3, DB, PC, RCT	1. Brexanolone 90 mcg/kg per hour IV over 60 hours (BX90) 3. Placebo IV over 60 hours (P)	Demographics: Age: 28 years Depression: 29% Previous PPD: 37% Baseline antidepressant use: 18% Average HAM-D score: 23 Key Inclusion Criteria:	mITT: 1. 51 2. 53 PP: 1. 48 2. 52 Attrition: 1. 6%	Change in 17-item HAM-D total score at 60 hours: BX90: -14.6 P: -12.1 LSMD -2.5 (95% CI, -4.5 to -0.5) p-value: 0.0160 Secondary Endpoints: CGI-I response:	NA	Discontinuations due to Adverse Events: BX90: 2 (4%) P: 0 Severe Adverse Event: BX90: 2 (4%) P: 1 (2%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) Randomized 1:1, baseline characteristics similar except for a higher number of patients in the placebo group with a history of depression compared to the treatment group, 33% and 24%, respectively. Performance Bias: See above Detection Bias: See above Attrition Bias: (low) low attrition in each group. Results analyzed with a mITT analysis.

		- 18-45 years - 6 months or less post-partum at screening with PPD - qualifying 17-item HAM-D score (20-25) Key Exclusion Criteria: - see above	2. 2%	BX90: 39 (80%) P: 29 (56%) BX90 vs. P: OR 5.0 (95% CI, 2.0 to 12.5) p-value: 0.0005	39/3			Reporting Bias: See above **Applicability**: Patient: Applies to women with moderate to severe depression, with or without current antidepressant use. Intervention: See above Comparator: See above Outcomes: See above Setting: See above
Abbreviations: ARR = absolute risk reduction; CGI =Clinical Global Impression-Improvement response; CI = confidence interval; HAM-D = Hamilton Rating Scale for Depression; LSMD= least squares mean difference; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PC = placebo controlled; PP = per protocol; PPD = post-partum depression								

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL status
amitriptyline HCl	AMITRIPTYLINE HCL	TABLET	Y
amitriptyline HCl	ELAVIL	TABLET	Y
bupropion HCl	BUPROPION HCL SR	TAB SR 12H	Y
bupropion HCl	WELLBUTRIN SR	TAB SR 12H	Y
bupropion HCl	BUPROPION HCL	TABLET	Y
citalopram hydrobromide	CITALOPRAM HBR	SOLUTION	Y
citalopram hydrobromide	CELEXA	TABLET	Y
citalopram hydrobromide	CITALOPRAM HBR	TABLET	Y
desipramine HCl	NORPRAMIN	TABLET	Y
desipramine HCl	DESIPRAMINE HCL	TABLET	Y
doxepin HCl	DOXEPIN HCL	CAPSULE	Y
doxepin HCl	DOXEPIN HCL	ORAL CONC	Y
escitalopram oxalate	ESCITALOPRAM OXALATE	TABLET	Y
escitalopram oxalate	LEXAPRO	TABLET	Y
fluoxetine HCl	FLUOXETINE HCL	CAPSULE	Y
fluoxetine HCl	PROZAC	CAPSULE	Y
fluoxetine HCl	FLUOXETINE HCL	SOLUTION	Y
fluoxetine HCl	FLUOXETINE HCL	TABLET	Y
fluoxetine HCl	SARAFEM	TABLET	Y
fluvoxamine maleate	FLUVOXAMINE MALEATE	TABLET	Y
imipramine HCl	IMIPRAMINE HCL	TABLET	Y
imipramine HCl	TOFRANIL	TABLET	Y
maprotiline HCl	MAPROTILINE HCL	TABLET	Y
mirtazapine	MIRTAZAPINE	TAB RAPDIS	Y
mirtazapine	REMERON	TAB RAPDIS	Y
mirtazapine	MIRTAZAPINE	TABLET	Y
mirtazapine	REMERON	TABLET	Y
nortriptyline HCl	NORTRIPTYLINE HCL	CAPSULE	Y
nortriptyline HCl	PAMELOR	CAPSULE	Y
nortriptyline HCl	NORTRIPTYLINE HCL	SOLUTION	Y
paroxetine HCl	PAROXETINE HCL	TABLET	Y
paroxetine HCl	PAXIL	TABLET	Y

protriptyline HCl	PROTRIPTYLINE HCL	TABLET	Y
sertraline HCl	SERTRALINE HCL	ORAL CONC	Y
sertraline HCl	ZOLOFT	ORAL CONC	Y
sertraline HCl	SERTRALINE HCL	TABLET	Y
sertraline HCl	ZOLOFT	TABLET	Y
trimipramine maleate	SURMONTIL	CAPSULE	Y
trimipramine maleate	TRIMIPRAMINE MALEATE	CAPSULE	Y
venlafaxine HCl	EFFEXOR XR	CAP ER 24H	Y
venlafaxine HCl	VENLAFAXINE HCL ER	CAP ER 24H	Y
venlafaxine HCl	VENLAFAXINE HCL	TABLET	Y
bupropion HBr	APLENZIN	TAB ER 24H	V
bupropion HCl	BUPROPION XL	TAB ER 24H	V
bupropion HCl	WELLBUTRIN XL	TAB ER 24H	V
bupropion HCl	FORFIVO XL	TAB ER 24H	V
clomipramine HCl	CLOMIPRAMINE HCL	CAPSULE	V
clomipramine HCl	ANAFRANIL	CAPSULE	V
desvenlafaxine	DESVENLAFAXINE ER	TAB ER 24	V
desvenlafaxine	KHEDEZLA	TAB ER 24	V
desvenlafaxine	DESVENLAFAXINE ER	TAB ER 24H	V
desvenlafaxine fumarate	DESVENLAFAXINE FUMARATE ER	TAB ER 24	V
desvenlafaxine succinate	DESVENLAFAXINE SUCCINATE ER	TAB ER 24H	V
desvenlafaxine succinate	PRISTIQ	TAB ER 24H	V
duloxetine HCl	CYMBALTA	CAPSULE DR	V
duloxetine HCl	DULOXETINE HCL	CAPSULE DR	V
escitalopram oxalate	ESCITALOPRAM OXALATE	SOLUTION	V
fluoxetine HCl	FLUOXETINE DR	CAPSULE DR	V
fluvoxamine maleate	FLUVOXAMINE MALEATE ER	CAP ER 24H	V
imipramine pamoate	IMIPRAMINE PAMOATE	CAPSULE	V
isocarboxazid	MARPLAN	TABLET	V
levomilnacipran HCl	FETZIMA	CAP SA 24H	V
levomilnacipran HCl	FETZIMA	CAP24HDSPK	V
nefazodone HCl	NEFAZODONE HCL	TABLET	V
paroxetine HCl	PAXIL	ORAL SUSP	V
paroxetine HCl	PAROXETINE CR	TAB ER 24H	V
paroxetine HCl	PAXIL CR	TAB ER 24H	V

paroxetine HCl	PAROXETINE ER	TAB ER 24H	V
paroxetine mesylate	PEXEVA	TABLET	V
phenelzine sulfate	NARDIL	TABLET	V
phenelzine sulfate	PHENELZINE SULFATE	TABLET	V
selegiline	EMSAM	PATCH TD24	V
tranylcypromine sulfate	TRANYLCYPROMINE SULFATE	TABLET	V
venlafaxine HCl	VENLAFAXINE HCL ER	TAB ER 24	V
vilazodone HCl	VIIBRYD	TAB DS PK	V
vilazodone HCl	VIIBRYD	TABLET	V
vortioxetine hydrobromide	TRINTELLIX	TABLET	V
amoxapine	AMOXAPINE	TABLET	
olanzapine/fluoxetine HCl	OLANZAPINE-FLUOXETINE HCL	CAPSULE	
olanzapine/fluoxetine HCl	SYMBYAX	CAPSULE	
trazodone HCl	TRAZODONE HCL	TABLET	

Appendix 2: Abstracts of Comparative Clinical Trials

Jacobsen PL, Mahableshwarkar AR, Chen Y, Chrones L, and Clayton AH. Effect of vortioxetine vs. escitalopram on sexual functioning in adults with well- treated major depressive disorder experiencing SSRI-induced sexual dysfunction.

Introduction: Sexual dysfunction is common with serotonergic antidepressants, including selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs), and does not resolve in most patients. Vortioxetine, an antidepressant with a multimodal mechanism of action, has shown low rates of sexual dysfunction in previous major depressive disorder (MDD) trials.

Aim: This study compared the effects of vortioxetine and escitalopram on sexual functioning in adults with well-treated MDD experiencing treatment-emergent sexual dysfunction (TESD).

Methods: Participants treated with, and responding to, citalopram, paroxetine, or sertraline were randomized to switch to either vortioxetine (10/20 mg; n = 225) or escitalopram (10/20 mg; n = 222) for 8 weeks. Sexual function was assessed using the Changes in Sexual Functioning Questionnaire Short Form (CSFQ-14), and antidepressant efficacy was assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS), Clinical Global Impressions (CGI) scale, and Profile of Mood States brief form (POMS-brief). Safety and tolerability were also assessed.

Main Outcome Measures: The primary endpoint was change from baseline in the CSFQ-14 total score after 8 weeks of treatment. The MADRS, CGI, and POMS-brief were used to assess antidepressant efficacy. Safety was assessed via adverse events, vital signs, electrocardiograms, laboratory values, weight, and physical examination findings.

Results: Vortioxetine showed significantly greater improvements in CSFQ-14 total score (8.8 ± 0.64, mean ± standard error) vs. escitalopram (6.6 ± 0.64; $P = 0.013$). Benefits vs. escitalopram were significant on four of five dimensions and all three phases of sexual functioning assessed by the CSFQ-14 ($P < 0.05$). Antidepressant efficacy continued in both groups, with similar, but slight, improvements in MADRS and CGI scores. Vortioxetine and escitalopram had similar clinical efficacy profiles in this study, with safety profiles similar to previous trials. Nausea (n = 9, 4.0%) was the most common treatment-emergent adverse event leading to discontinuation of vortioxetine.

Conclusion: Switching antidepressant therapy to vortioxetine may be beneficial for patients experiencing sexual dysfunction during antidepressant therapy with SSRIs.

Appendix 3: Medline Search Strategy

Database(s): Ovid MEDLINE(R) 1946 to April Week 1 2019
Search Strategy:

#	Searches	Results
1	amitriptyline.mp. or Amitriptyline/	8629
2	bupropion.mp. or Bupropion/	4249
3	citalopram.mp. or Citalopram/	6187
4	desipramine.mp. or Desipramine/	7653
5	doxepine.mp.	86
6	escitalopram.mp. or Citalopram/	5085
7	fluoxetine.mp. or Fluoxetine/	12328
8	fluvoxamine.mp. or Fluvoxamine/	2686
9	imipramine.mp. or Imipramine/	12752
10	maprotiline.mp. or Maprotiline/	1259
11	mirtazapine.mp. or Mirtazapine/	1873
12	nortriptyline.mp. or Nortriptyline/	2930
13	paroxetine.mp. or Paroxetine/	5672
14	protriptyline.mp. or Protriptyline/	399
15	sertraline.mp. or Sertraline/	4304
16	trimipramine.mp. or Trimipramine/	494
17	venlafaxine.mp. or Venlafaxine Hydrochloride/	3682
18	clomipramine.mp. or Clomipramine/	3766
19	desvenlafaxine.mp. or Desvenlafaxine Succinate/	348
20	duloxetine.mp. or Duloxetine Hydrochloride/	2051
21	isocarboxazid.mp. or Isocarboxazid/	404
22	levomilnacipran.mp.	54
23	nefazodone.mp.	727
24	phenelzine.mp. or Phenelzine/	1595
25	selegiline.mp. or Selegiline/	2723
26	tranylcypromine.mp. or Tranylcypromine/	2172

27	venlafaxine.mp. or Venlafaxine Hydrochloride/	3682
28	vilazodone.mp. or Vilazodone Hydrochloride/	148
29	vortioxetine.mp. or Vortioxetine/	249
30	amoxapine.mp. or Amoxapine/	436
31	trazodone.mp. or Trazodone/	1845
32	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31	66706
33	limit 32 to (english language and humans)	39890
34	limit 33 to yr="2017 -Current"	1640
35	limit 34 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	155

Appendix 4: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

SPRAVATO™ (esketamine) nasal spray, CIII
Initial U.S. Approval: 1970 (ketamine)

WARNING: SEDATION; DISSOCIATION; ABUSE AND MISUSE; and SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning.

- **Risk for sedation and dissociation after administration. Monitor patients for at least two hours after administration. (5.1, 5.2)**
- **Potential for abuse and misuse. Consider the risks and benefits of prescribing SPRAVATO prior to using in patients at higher risk of abuse. Monitor patients for signs and symptoms of abuse and misuse. (5.3)**
- **SPRAVATO is only available through a restricted program called the SPRAVATO REMS. (5.4)**
- **Increased risk of suicidal thoughts and behaviors in pediatric and young adult patients taking antidepressants. Closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors. SPRAVATO is not approved for use in pediatric patients. (5.5)**

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

SPRAVATO™ is a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist indicated, in conjunction with an oral antidepressant, for the treatment of treatment-resistant depression (TRD) in adults. (1)

Limitations of Use: SPRAVATO is not approved as an anesthetic agent. The safety and effectiveness of SPRAVATO as an anesthetic agent have not been established. (1)

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

- Administer SPRAVATO intranasally under the supervision of a healthcare provider. (2.1)
- Assess blood pressure prior to and after administration. (2.1)
- Evidence of therapeutic benefit should be evaluated at the end of the induction phase to determine need for continued treatment. (2.2)
- See Full Prescribing Information for recommended dosage during the induction and maintenance phases. (2.2)
- See Full Prescribing Information for important administration instructions. (2.3)

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

Nasal Spray: 28 mg of esketamine per device. Each nasal spray device delivers two sprays containing a total of 28 mg of esketamine. (3)

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

- Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial and peripheral arterial vessels) or arteriovenous malformation. (4)
- Intracerebral hemorrhage. (4)
- Hypersensitivity to esketamine, ketamine, or any of the excipients. (4)

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

- *Increases in Blood Pressure:* Patients with cardiovascular and cerebrovascular conditions and risk factors may be at an increased risk of associated adverse effects. (5.6)
- *Cognitive Impairment:* SPRAVATO may impair attention, judgment, thinking, reaction speed and motor skills. (5.7)
- *Impaired Ability to Drive and Operate Machinery:* Do not drive or operate machinery until the next day after a restful sleep. (5.8)
- *Embryo-fetal Toxicity:* May cause fetal harm. Consider pregnancy planning and prevention in females of reproductive potential. (5.10, 8.1, 8.3)

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

The most commonly observed adverse reactions (incidence ≥5% and at least twice that of placebo plus oral antidepressant) were dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, blood pressure increased, vomiting, and feeling drunk. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Pharmaceuticals, Inc. at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

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

- Lactation: Breastfeeding not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 03/2019

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ZULRESSO™ (brexanolone) injection, for intravenous use, [controlled substance schedule pending]
Initial U.S. Approval: [pending controlled substance scheduling]

WARNING: EXCESSIVE SEDATION AND SUDDEN LOSS OF CONSCIOUSNESS

See full prescribing information for complete boxed warning.

- **Patients are at risk of excessive sedation or sudden loss of consciousness during administration of ZULRESSO. (5.1)**
- **Because of the risk of serious harm, patients must be monitored for excessive sedation and sudden loss of consciousness and have continuous pulse oximetry monitoring. Patients must be accompanied during interactions with their child(ren). (5.1)**
- **ZULRESSO is available only through a restricted program called the ZULRESSO REMS. (5.1, 5.2)**

INDICATIONS AND USAGE

ZULRESSO is a neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator indicated for the treatment of postpartum depression (PPD) in adults. (1)

DOSAGE AND ADMINISTRATION

- A healthcare provider must be available on site to continuously monitor the patient, and intervene as necessary, for the duration of the infusion (2.1).
- Administered as a continuous intravenous infusion over 60 hours (2.5 days) as follows (2.2):
  - 0 to 4 hours: Initiate with a dosage of 30 mcg/kg/hour
  - 4 to 24 hours: Increase dosage to 60 mcg/kg/hour
  - 24 to 52 hours: Increase dosage to 90 mcg/kg/hour (alternatively consider a dosage of 60 mcg/kg/hour for those who do not tolerate 90 mcg/kg/hour)
  - 52 to 56 hours: Decrease dosage to 60 mcg/kg/hour
  - 56 to 60 hours: Decrease dosage to 30 mcg/kg/hour
- Dilution required prior to administration. (2.3)

DOSAGE FORMS AND STRENGTHS

Injection: 100 mg/20 mL (5 mg/mL) single-dose vial. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

Suicidal Thoughts and Behaviors: Consider changing the therapeutic regimen, including discontinuing ZULRESSO, in patients whose PPD becomes worse or who experience emergent suicidal thoughts and behaviors. (5.3)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) were sedation/somnolence, dry mouth, loss of consciousness, and flushing/hot flush. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sage Therapeutics, Inc. at 1-844-4-SAGERX (1-844-472-4379) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

USE IN SPECIFIC POPULATIONS

- Pregnancy: May cause fetal harm. (8.1)
- Avoid use in patients with end stage renal disease (ESRD). (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 3/2019

Appendix 5: Key Inclusion Criteria

Population	Patients with major depressive disorder, anxiety disorder or post-traumatic stress disorder
Intervention	Antidepressant
Comparator	Placebo or active treatment comparison
Outcomes	Symptom improvement, response or remission of depression
Timing	At onset of symptoms
Setting	Outpatient and inpatient (brexanolone)

Appendix 6: Proposed Safety Edits

Brexanolone (Zulresso)

Goal(s):

- To ensure appropriate use of brexanolone in patient with post-partum depression.

Length of Authorization:

One time use only.

Requires PA:

- Brexanolone requires a prior authorization approval due to safety concerns (pharmacy and physician administered claims)

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP

Approval Criteria		
4. Is the patient an adult with moderate to severe post-partum depression?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Has the patient had an adequate trial (6-8 weeks) of an oral antidepressant?	**Yes:** Approve for a single, continuous, intravenous infusion over 60 hours (titrated per prescribing recommendations)	**No:** Pass to RPh. Deny; recommend trial of oral antidepressant

P&T/DUR Review: 7/19 (KS)
Implementation: TBD

Esketamine (Spravato)

Goal(s):

- To ensure safe and appropriate use of esketamine in patients with treatment resistant depression.

Length of Authorization:

Up to 6 months

Requires PA:

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

Covered Alternatives:

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

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

Approval Criteria		
2. Is this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Is the request for maintenance dosing of esketamine (for determining response to therapy)?	**Yes:** Go to #9	**No:** Go to #5
5. Is the patient 65 years or older?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #6
6. Does the patient have treatment resistant depression (failure of two antidepressants which were given for at least 6-8 weeks at FDA approved doses)?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness. Recommend an adequate trial (minimum of 6-8 weeks) of 2 or more antidepressants.
7. Is the patient currently on an FDA approved dose of an oral antidepressant?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness. Esketamine is indicated for use with an oral antidepressant.
8. Does the patient have documentation of any of the following: • Aneurysmal vascular disease or arterial venous malformation OR • Intracerebral hemorrhage OR • Pregnancy OR • Uncontrolled hypertension	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve for induction phase only: 28 days of treatment with a maximum of 23 nasal spray devices (each device contains 28 mg of esketamine)

Approval Criteria		
9. Is there documentation that the patient demonstrated an adequate response during the induction phase (an improvement in depressive symptoms)?	**Yes:** Approve for up to 6 months (maximum of 12 per month)	**No:** Pass to RPh. Deny; medical appropriateness.

P&T/DUR Review: 7/19 (KS)
Implementation: TBD

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

New Drug Evaluations: Drugs for Polyneuropathy of Hereditary Transthyretin-Mediated Amyloidosis

Date of Review: July 2019

Generic Name: patisiran
Brand Name (Manufacturer): Onpattro™ (Alnylam Pharmaceuticals Inc.)

Generic Name: inotersen
Brand Name (Manufacturer): Tegsedi™ (Ionis Pharmaceuticals, Inc.)

Purpose for Class Update:
To evaluate the evidence for efficacy and safety of patisiran and inotersen in the treatment of polyneuropathy associated with hereditary transthyretin-mediated amyloidosis (hATTR).

Research Questions:
1. Is patisiran safe and effective in improving clinically meaningful outcomes, including improvements in disease progression, quality of life, and survival in patients with hATTR?
2. Is inotersen safe and effective in improving clinically meaningful outcomes, including improvements in disease progression, quality of life, and survival in patients with hATTR?
3. Are there subgroups of patients with hATTR for which patisiran or inotersen is more effective or associated with fewer adverse events?

Conclusions:
- There is low quality evidence, based on one randomized controlled trial with high risk of bias, that patisiran may improve neurologic impairment in polyneuropathy of hATTR, demonstrated by a statistically significant reduction in the modified neurologic impairment score (mNIS + 7) compared to placebo (-6 points versus +28 points; mean difference -34 points; 95% Confidence Interval [CI] -39.9 to -28.1).[1] However, it remains unknown if this difference in the mNIS + 7 is clinically relevant or noticeable to the patient since this outcome has not been validated or used in other clinical trials.
- There is low quality evidence that patisiran modestly improves quality of life compared to placebo in patients with polyneuropathy of hATTR, as measured by the Norfolk-Quality of Life-Diabetic Neuropathy Scale (Norfolk-QoL-DN) (-6.7 vs. 14.4; least squares [LS] mean difference -21.1; 95% CI -27.2 to -15.0).[1] This scale has been validated for use in patients with Transthyretin Familial Amyloid Polyneuropathy (TTR-FAP), but there is not a defined minimum clinically important difference.
- There is insufficient evidence that patisiran decreases cardiovascular outcomes or improves survival and does not improve disease progression or ambulation compared to placebo.
- There did not appear to be an increase in serious adverse events, death or discontinuations due to adverse events with patisiran compared to placebo. However, long term safety of patisiran, which is the first in its class, is unknown due to insufficient data.
- There is low quality evidence, based on one randomized controlled trial with high risk of bias, that inotersen slows the progression of neurologic impairment compared to placebo, measured by the change in mNIS+7 score from baseline (+5.8 points vs. +25.5 points; treatment different -19.7; 95% CI -26.4 to -13)

Author: Megan Herink, Pharm.D.

and stabilizes quality of life, measured by the Norfolk-QoL-DN (1 point vs. 12.7 points; treatment difference -11.7; 95% CI -18.3 to -5.1).[2] The clinical significance associated with these changes is unknown.

- There is insufficient evidence that inotersen decreases cardiovascular outcomes or improves survival and does not improve disease progression.
- There are significant safety concerns associated with inotersen, including severe thrombocytopenia, potentially irreversible glomerulonephritis, hepatic accumulation, and neurotoxicity. Based on only one small clinical trial, the magnitude of harm remains unknown at this time.
- It is difficult to generalize results of available studies to the United States (U.S.) population with a low number of U.S. participants included in trials. Very few patients with the most common hATTR genotype in the U.S. (Val122Ile) were included in clinical trials for patisiran (0.9%) and inotersen (1.7%)

Recommendations:

- Create Preferred Drug List (PDL) class for Drugs for hATTR.
- Designate inotersen and patisiran as non-preferred medications.
- Implement clinical prior authorization criteria for patisiran and inotersen to ensure appropriate utilization (**Appendix 2**).

Background:

Hereditary transthyretin amyloidosis (hATTR) is a rare, progressive, and fatal autosomal dominant disorder caused by misfolding deposits of transthyretin (TTR), a protein produced by the liver that normally functions as a transporter of thyroxine and retinol (vitamin A).[3] The disorder presents in a spectrum of clinical presentations due to amyloid deposits, including a predominantly neurologic phenotype (familial amyloid polyneuropathy [FAP]) and a predominantly cardiac phenotype (familial cardiomyopathy [FAC]). However, hATTR can present with both cardiac and neurologic manifestations. There are over 120 TTR reported mutations. Some mutations are more strongly associated with polyneuropathy (V30M) and some with cardiomyopathy.[4] The most common mutation in the U.S. is the V122I mutation, which typically leads to cardiomyopathy.[5] The second most common mutation in the U.S. is T60A, which causes a mixed neuropathy and cardiomyopathy presentation.[5] Deterioration in activities of daily living and ambulation are seen due to neuropathic changes as well as autonomic dysfunction. Additionally, hATTR can affect multiple organ systems resulting in weight loss, wasting, difficulty walking, and alternating constipation and diarrhea, often due to autonomic nerve involvement. Cardiac manifestations can include heart failure, arrhythmias, orthostatic hypotension or sudden death due to severe conduction disorders. Survival of 5 to 15 years is expected after the onset of FAP and only 2 to 5 years for those with cardiomyopathy. The exact incidence is unknown but is estimated to be 1/100,000 in U.S. Caucasians.[6] The estimated worldwide prevalence of FAP is 5,000 to 10,000 with approximately 100 to 2500 individuals in the US.[6] Symptoms of FAP typically appear between 30 and 55 years of age. Death is commonly a result of cardiac dysfunction, infection or cachexia.[6]

Standard of care for hATTR has been limited to liver transplantation and administration of transthyretin tetramer stabilizers.[7] Liver transplant has been the treatment of choice for those with neuropathy but no cardiac involvement. Transplantation is most effective when initiated early in the course of the disease in those with V30M mutations. Other treatment options for hATTR-associated polyneuropathy include tafamidis and diflunisal; however, neither medication was FDA approved in the U.S. for FAP until recently. Diflunisal, a non-steroidal anti-inflammatory (NSAID), is used off-label in the U.S, but long-term use is limited due to risks associated with NSAIDs, including gastrointestinal bleeding, renal insufficiency and cardiovascular events. More recently, tafamidis was FDA approved for the cardiomyopathy phenotype and will be reviewed at a future meeting. Both drugs have been shown to slow progression of neurologic impairment to a small extent.

The goal of treatment is to stabilize disease progression and potentially reverse neuropathy, as well as improve quality of life. There is no established test or study outcome that has been found to be adequate in quantifying disease severity and overall symptom burden of hATTR. The Neurologic Impairment Scale

[NIS] +7 , the primary study outcome in clinical trials, was modified from scales used in tafamidis and diflunisal trials to better reflect overall symptoms and impairment of hATTR.[4] These are described in more detail below; however, it remains difficult to quantify a meaningful change in these complex outcomes and how it relates to disease progression and overall perceived benefit to the patient. Additionally, these complicated and time-consuming assessments are subject to variability between investigators and extensive training is required.

RNA interference (RNAi) is a naturally occurring cellular mechanism for regulating gene expression that is mediated by small interfering ribonucleic acids. Newer agents, including patisiran, are RNAi agents that reduce the production of transthyretin by targeting the untranslated region of transthyretin mRNA in the liver.[6] Patisiran was the first agent approved for treatment of hATTR and was granted breakthrough designation by the FDA in 2018 after initial denial in 2013 due to discussion of the modified primary outcomes.[6] Patisiran is approved for polyneuropathy associated with hATTR and is administered intravenously (IV) every three weeks. Inotersen is an antisense oligonucleotide that binds TTR messenger RNA and induces its degradation. It is administered as a once weekly subcutaneous injection.[8] Both of these agents are only approved for the FAP phenotype of hATTR.

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.

Systematic Reviews:
None identified

New Guidelines:
There were no clinical guidelines identified that include either patisiran or inotersen.

NEW DRUG EVALUATION: Patisiran (Onpattro™)

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

Clinical Efficacy:
Patisiran was FDA approved for polyneuropathy of hATTR based on one phase 3, randomized, double-blind, placebo-controlled trial evaluating patisiran IV every 21 days compared to matched placebo for 18 months.[1] Subjects in the trial were required to have a NIS of 5 to 130. The NIS ranges from 0 to 244, with higher scores indicating more impairment. The inclusion range was carefully selected to include patients with disease advanced enough to have progression in the placebo group, but not so advanced to mask a treatment effect.[4] Subjects also had to have a polyneuropathy disability (PND) score of IIIb or lower and adequate

liver and renal function. The PND score is a five-stage measure of neuropathy impairment ranging from 0 (no impairment) from 4 (confined to wheelchair or bedridden). Full inclusion and exclusion criteria can be found in the evidence table (**Table 4**).

There was a statistically significant difference in baseline TTR genotype with 52% of patients in the placebo group having the V30M genotype and only 38% of patients in the patisiran group.[1] This is the most common genotype that is associated with early onset disease and has the highest response rates to liver transplantations. However, this genotype is less prevalent in the U.S. Additionally, the mean baseline NIS score was 3.5 points higher in the patisiran group, indicating more severe impairment, compared to the placebo group. Lastly, patients in the patisiran group had more cardiac manifestations (61%) compared to placebo (47%). These baseline differences increase the risk of bias and could reflect differences in disease severity at baseline and impact the ability to compare the two groups. Additional limitations that contribute to an increased risk of bias include an unequal attrition rate in the patisiran group (7%) versus placebo (29%) and possible unblinding due to infusion related reactions.[1] More patients in the placebo group discontinued study drug due to adverse events (9% vs. 2%) and due to disease progression (5% vs. < 1%) compared to patisiran. However, nearly half of discontinuations were unexplained and it is not clear why many placebo patients discontinued study treatment.

The primary outcome was change from baseline in the modified neurologic impairment score (mNIS+7) at 18 months.[1] Response to treatment was defined as a less than 10-point increase from baseline. This includes a clinical exam-based exam of neurologic impairment combined with electrophysiologic measures of small and large nerve fiber function and measurement of autonomic function (postural blood pressure). The mNIS+7 used in this trial was modified from the original NIS+7 to better assess total body sensation, autonomic function, and nerve conduction.[4] This is a very complex 304 point assessment tool that includes multiple scoring components (presented in **Table 1**) and required training of neuromuscular physicians.[4] While an increase in total score indicates worsening impairment, it is unclear how to evaluate changes in the score and what constitutes a clinically meaningfully improvement. Additionally, this score was modified and has not been validated or used in previous clinical trials. Older neuropathy impairment assessment tools do have defined minimal clinically important differences but were determined to be unsuccessful in reflecting neuropathic symptoms from hATTR.[3] The FDA clinical reviewer noted that many of the individual components of the score (nerve conduction) are biomarkers that do not, by themselves, represent direct clinical benefit.[6] Additionally, differences in other components of the score (motor and sensory function by neurologic exam) detected by the physician might not be not noticeable to the patient or result in improved function in daily activities.[6] The FDA reviewer suggested results would need to be evaluated in context of results secondary endpoints.

A secondary outcome was quality of life, measured by the Norfolk-Quality of Life-Diabetic Neuropathy Scale (Norfolk-QoL-DN). This is a 35- item patient-reported measure that evaluates patients' perception of impairment and was originally developed to assess patients' perceptions of symptoms associated with diabetic neuropathy.[10] It has a maximum possible score of 136, with higher scores indicating greater impairment, or worse quality of life. This scale has been validated for use in patients with TTR-FAP, but there is not a defined minimum clinically important difference.[10]

Table 1: Modified Neurologic Impairment Scores Used as Primary Outcomes in Trials of Patisiran and Inotersen

	APOLLO Trial (Patisiran)	**NEURO-TTR (Inotersen)**
Total Score	304	346.3
Assessment (Score)		
Motor strength/weakness	Neurologic exam (192)	Neurologic exam (192)
Reflexes	Neurologic exam (20)	Neurologic exam (20)
Sensation	Quantitative sensory testing (80)	Quantitative sensory testing (80) + additional sensations (32)

Composite nerve conduction score	Σ5 – ulnar compound muscle action potential (CMAP) and sensory nerve action potential (SNAP), peroneal CMAP, tibial CMAP, sural SNAP (10)	-18.6 points to 18.6 points
Autonomic function	Postural blood pressure (2)	Heart rate response to deep breathing (-3.72 points to 3.72 points)

Overall, there was a statistically significant change from baseline in the mNIS+7 with patisiran compared to placebo (-6.0 vs. 28; LS mean difference, -34.0 points; 95% CI -39.9 to 28.1), indicating a potential improvement in neurological function in the patisiran group and a worsening in the placebo group.[1] The clinical significance of a change in 6 points is unclear. However, the FDA notes that this observed improvement is not consistent with the natural history of the disease.[6] The effect was largely driven by muscle strength and quantitative sensory testing (QST). Strength testing could also be affected by changes in motivation by the subject or provider. However, QST is unlikely to be affected by motivation. Significantly more patients in the patisiran group experienced neurologic improvement compared to placebo (56% vs. 4%; ARR 52%; NNT 2), defined as a decrease in mNIS+7.

There was also a statistically significant difference in quality of life, measured by change from baseline in Norfolk-QoL-DN, in the patisiran group compared to placebo (-6.7 vs. 14.4; LS mean difference -21.1; 95% CI -27.2 to -15.0).[1] Patients on patisiran showed modest improvements in physical function/large fiber neuropathy, symptoms and autonomic domains while placebo patients reported worsening in all five domains.

There were statistically significant differences in all secondary polyneuropathy outcomes including: disability (Rasch-built Overall disability scale), gait speed (10-meter walk test), nutritional status (modified-body mass index), and an assessment score of autonomic symptoms (COMPASS 31), consistent with the positive findings of the primary outcome.[1] These were all measured by scales with unclear minimum clinical differences. The difference in gait speed from the 10-MWT was 0.311 meters per second.[1] Disease progression was measured by the polyneuropathy disability score (PND) and FAP stage. FAP stage remained stable in 76% of patisiran patients and only 5 (3%) of patients reported improved FAP stage.[9] No placebo patient reported improved FAP stage, but the groups were not statistically compared. Additionally, ambulation (PND score) only improved in 12 (8%) of patisiran patients and 0 of the placebo patients.[9] There is insufficient evidence to make conclusions on the effect of patisiran on cardiovascular outcomes in patients with cardiovascular manifestations.

Only 20% of patients were from the U.S., which has a different genotype mix than other countries, limiting generalizability to the U.S. population. There were very few patients with the most common genotype found in the U.S. (Val122Ile). This trial was not designed to demonstrate patients improved on treatment and FDA approval was largely based on the idea that any improvement from baseline is inconsistent with the natural history of the disease.[6] Long-term benefits and effects on survival are unclear.

Clinical Safety:
The most common adverse events associated with patisiran were upper respiratory infections and infusion reactions (**Table 2**). Discontinuations due to adverse events were more common in the placebo group than patisiran. There were four serious adverse events of atrioventricular block in the patisiran group. There did not appear to be a difference in overall deaths between the two groups (5% vs. 8%) and all deaths in the patisiran group were due to cardiovascular causes. This could be due to the natural history of the disease; but the causes of deaths in the placebo group were variable.

Table 2: Adverse Reactions Occurring in at least 5% of Patisiran-treated Patients and More Frequently Than Placebo

	Patisiran	Placebo
Peripheral edema	30%	22%
Upper respiratory tract infections	29%	21%
Infusion related reaction	19%	9%
Dyspepsia	8%	4%
Muscle spasms	8%	1%
Arthralgia	7%	0
Dyspnea	7%	0
Erythema	7%	3%
Bronchitis	7%	3%
Vertigo	5%	1%

Table 3. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Patisiran is a double-stranded siRNA that causes degradation of mutant and wild-type TTR mRNA through RNA interference, which results in a reduction of serum TTR protein and TTR protein deposits in tissues
Oral Bioavailability	N/A - Administered intravenously
Distribution and Protein Binding	Distributed primarily in the liver. Protein binding is low (<2.1%)
Elimination	<1% excreted unchanged in urine
Half-Life	3 days
Metabolism	Metabolized by nucleases to shorter nucleotides.

Abbreviations: mRNA: messenger RNA; N/A: not applicable; siRNA: small interfering ribonucleic acid; TTR: transthyretin

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Quality of life
2) Functional Improvement
3) Disease Progression
4) Survival
5) Serious adverse events
6) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Change from baseline in modified NIS+7 score at 18 months

Table 4. Comparative Evidence Table.

Ref./Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. APOLLO[1,4] PC, MC, DB, RCT	1. Patisiran 0.3 mg/kg IV Q 21 days 2. Placebo (0.9% NACL) All patients received the following pre-medications: -Dexamethasone IV (10 mg) or equivalent, - Oral APAP 500 mg -Intravenous H2 blocker -intravenous H1 blocker (diphenhydramine 50 mg or equivalent) Duration: 21 months	Demographics: Patients with hATTR polyneuropathy Mean mNIS+7 (80.9 patisiran, 74.6 placebo) Median age 62 74% male, stage 1 FAP 46.2%, Val30Met: 42.7% Key Inclusion Criteria: Age 18-85, diagnosis of hATTR with peripheral neuropathy, NIS of 5 to 130, Karnofsky performance status* of ≥ 60%, ANC ≥ 1500, platelet ≥ 100,000, Hg ≥ 10 g/dl, AST/ALT < 2.5 x ULN, normal bilirubin, albumin ≥ 3 g/dl INR ≤ 1.2, Scr ≤1.5 x ULN, negative HBV and HCV, negative pregnancy test, 2 methods of contraception Key Exclusion Criteria: Low vitamin A or B12 levels, liver transplant, type 1 diabetes or type 2 diabetes for ≥5 years, HIV, heart failure, recent ACS, unstable angina, anticipated survival < 2 years, use of TTR stabilizers (tafamidis, diflunisal)	Randomized: 148 77 mITT: 141 67 PP: 137 51 Attrition: 29 (38%) 11 (7%)	Primary Endpoint: Change from baseline in mNIS+7 (least squares mean change [SE]) 1. -6.0±1.7 2. 28.0±2.6 Difference -34.0 points; (95% CI -39.9 to -28.1) P<0.001 Improvement in mNIS+7 1. 56% 2. 4% OR 39.9; (95% CI 11-144.4) P<0.01 Secondary Endpoints: Quality of life (change from baseline in Norfolk QOL-DN questionnaire) 1. -6.7±1.8 2. 14.4±2.7 LS mean difference -21.1 points; (95% CI -27.2 to -15) P<0.001 Improvement in Norfolk-QOL-DN: 1. 51.4% 2. 10.4% OR 10.0; (95% CI 4.4 to 22.5)	NA ARR 52%; NNT 2 NA ARR 41%; NNT 3	D/C due to AE: 1. 3 (2.0%) 2. 7 (9.1%) Death: 1. 7 (4.7%) 2. 6 (7.8%) Infusion-related reaction: 1. 28 (19%) 2. 7 (9%) P values and 95% CI not reported	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: High; randomization via interactive response system; treatment concealed to all but unblinded personnel. However, significant differences in baseline characteristics between groups (TTR genotype, baseline NIS score, cardiac involvement, etc.) Performance Bias: Unclear; double-blinded to patient and provider, double-dummy design. However, possibility of unblinding due to infusion related reactions. Detection Bias: Low; Personnel blinded to lab results that could unblind treatment (vitamin A, thyroid tests, etc.) Attrition Bias: High; modified ITT population was only used for secondary and exploratory outcomes. The primary endpoint and first secondary endpoint were analyzed using the PP population and missing data were not imputed; high and unequal attrition in each group. Nearly half of discontinuations were unexplained. Reporting Bias: Low. All pre-specified outcomes reported Other Bias: high; Protocol and statistical analysis plan was developed by Alnylam Pharmaceuticals. Sponsor-employed authors were involved in analyzing the data and preparing the first draft. Editorial assistance was provided by Adelphi Communications, under contract with Alnylam Pharmaceuticals. **Applicability**: Patient: Under representation of US patients and genotype most common in the US (VAL122Ile mutation). Extensive exclusion criteria also limits generalizability. Intervention: Patisiran IV Q 21 days. There are no data to evaluate a dose-response with respect to clinical efficacy. Comparator: Placebo as comparator. No appropriate active comparator based on lack of FDA approved treatments. Outcomes: Complex outcome measures used which are difficult to interpret. Lack of clinically meaningful outcomes. Setting: 46 sites across 19 countries (US, France, Taiwan, Spain, Japan, Germany, Mexico, Portugal, South Korea, Sweden, Bulgaria, Italy, Canada, Turkey, Cyprus, Brazil, Netherlands, UK, Argentina). 21% of patients in North America, but distribution uneven between groups (13% vs. 25%)

Abbreviations [alphabetical order]: ACS = acute coronary syndrome; AE =adverse effects; ANC = absolute neutrophil count; APAP = acetaminophen; ARR = absolute risk reduction; CI = confidence interval; DB = double-blind; D/C = discontinuation; FAP = familial amyloid polyneuropathy; ITT = intention to treat; H2 = histamine 2; hATTR = hereditary transthyretin-mediated amyloidosis; HBV = hepatitis B virus; HCV = hepatitis C virus; Hg = hemoglobin; HIV = human immunodeficiency virus; IV= intravenous; MC = multi-center; mITT = modified intention to treat; mNIS = modified neuropathic impairment score; N = number of subjects; NA = not applicable; NaCl = normal saline; NNH = number needed to harm; NNT = number needed to treat; OR = odds ratio; PC = placebo controlled; PP = per protocol; RCT = randomized controlled trial; SE = standard error; TTR = transthyretin; ULN = upper limit of normal
*Karnofsky performance status measures a patient's functional status and ranges from 0 to 100 (0=death and 100 = normal function)

NEW DRUG EVALUATION: Inotersen (Tegsedi™)

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

Clinical Efficacy:
Inotersen was FDA approved based on one phase 3, randomized, double-blind, placebo-controlled trial comparing inotersen 300 mg weekly subcutaneous injection to placebo for 15 months in patients hATTR patients with polyneuropathy.[2] Similar to the previous trial evaluating patisiran, patients had to have a baseline NIS of 10 to 130. Patients received three injections in the first week, followed by weekly injections and all patients received vitamin A supplementation. Fifty-two percent of patients had the Val30M TTR mutation and the majority of patients were still ambulatory (67%).[2]

The primary endpoints were the same as the patisiran trial (mNIS+7 and Norfolk-QOL-DN) and are described in detail above. However, the mNIS+7 was modified slightly differently in this trial compared to the patisiran trial (**Table 1**). A lower score represents better neurologic function, and there is insufficient data to suggest a minimum clinically important difference for either scale. The authors of the trial suggest a 2-point difference as being clinically significant.[2] However, the studies cited for this statement evaluated the original NIS and NIS+7 scales and are not applicable to the modified scale used in this study.

Differences in baseline characteristics (**Table 7**) increase the risk of bias. Patients in the inotersen group had more severe sensorimotor and autonomic neuropathy, a higher baseline mNIS + 7 (79.35 vs. 74.12), and a higher proportion of patients with cardiac symptoms compared to placebo (67% vs. 55%).[8] Additionally, discontinuation rates were relatively high and differed between inotersen (22.3%) and placebo (13.3%).Only 3 patients (1.7%) had the Val122Ile mutation, the most common genotype seen in the U.S.

There was a significant difference in the primary outcome, change in mNIS+7 from baseline, between inotersen and placebo (treatment difference -19.7; 95% CI -26.4 to -13).[2] Both groups experienced neuropathy progression from baseline, but the inotersen group experienced a reduced level of progression in mNIS +7 (5.8 points) compared to placebo (25.5 points).[2] More patients in the inotersen group experienced an improvement in mNIS+7 compared to placebo (36.5% vs. 19.2%).[2] Similarly, there was a statistically significant difference in quality of life scores between inotersen and placebo (treatment difference -11.7; 95% CI -18.3 to -5.1) and significantly more patients in the inotersen group reported improvement in quality of life compared to placebo (50% vs. 26.9%). Still, half of the patients receiving inotersen did not report any improvement. It is uncertain if these treatment differences correlate to a clinically meaningful improvement for patients.

There were no differences in disease progression, measured by the polyneuropathy disability score (PND), a five-stage measure of neuropathy impairment ranging from 0 (no impairment) to 4 (confined to a wheelchair or bedridden).[9] Although it was not compared statistically, more patients in the placebo group reported improvements or stabilization in the PND score (65% vs. 58%). Comparable proportions of patients in the two groups reported a worsening in disease stage. There was also no significant difference in modified body mass index.

Clinical Safety:
The most common side effects occurring in 10% or more of patients and twice as frequently as placebo are included in **Table 5**. There were more discontinuations due to adverse effects (13% vs. 2%) and more serious adverse events (32% vs. 22%) in the inotersen group compared to placebo, respectively.

There were 5 deaths in the inotersen group and zero in the placebo group. Four were considered related to disease progression and one possibly from the drug (intracranial hemorrhage associated with severe thrombocytopenia). Two significant safety concerns associated with inotersen include severe thrombocytopenia and glomerulonephritis. Decreased platelet count occurred in 54% of inotersen patients compared to 13% of placebo patients and platelet counts less than 100 X 10^9/L occurred in 25% of inotersen patients, compared with 2% of placebo patients.[8] Glomerulonephritis occurred in 3 patients (3%) treated with inotersen and no patients on placebo. Additional safety concerns include liver toxicity, inflammatory and immune changes, and CNS toxicity (arterial dissection, stroke).[8] In these patients, stopping inotersen alone was not sufficient to correct glomerulonephritis. Additionally, seven patients stopped inotersen due to hypersensitivity reactions associated with antibody formation to inotersen. FDA review recommended post-marketing studies to further evaluate the risks of thrombocytopenia, glomerulonephritis and neurologic toxicity using a Risk Evaluation and Mitigation Strategies (REMS) program. Additional warnings and precautions are included in the drug label. Based on available data and long half-life of inotersen (32 days), the magnitude for serious harm remains unknown.

Table 5: Adverse Events See in Inotersen Trial

	Inotersen (n=112)	**Placebo (n=60)**
Decreased Platelets	54%	13%
Nausea	31%	12%
Headache	23%	12%
Pyrexia	20%	8%
Vomiting	15%	5%
Anemia	13%	3%
Thrombocytopenia	13%	2%

Table 6. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Inotersen is an antisense oligonucleotide that causes degradation of mutant and wild-type TTR mRNA through binding to the TTR mRNA, which results in a reduction of serum TTR protein and TTR protein deposits in tissues.
Oral Bioavailability	N/A; subcutaneous injection
Distribution and Protein Binding	Highly bound to plasma proteins (>94%); rapidly distributes to tissues, with the highest concentrations seen in the kidney and liver (volume of distribution 293 L)
Elimination	Cleared through metabolism; < 1% excreted unchanged in urine
Half-Life	32.3 days
Metabolism	Metabolized by nucleases to shorter nucleotides.

Abbreviations: mRNA: messenger RNA; TTR: transthyretin

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Quality of life
2) Functional Improvement
3) Survival
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Change from baseline in modified NIS+7 score at week 66
2) Change in baseline in Norfolk QOL-DN at week 66

Table 7: Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. NEURO-TTR[2] PC, DB, MC, RCT	1. 300 mg Inotersen SQ once a week 2. Placebo SQ once a week Duration: 15 months	Demographics: Patients with hATTR polyneuropathy Mean mNIS+7 (79.2 inotersen, 74.8 placebo) Median age 59 69% male; 92% white, stage 1 FAP 66%; Val30Met: 42.7% Key Inclusion Criteria: Age 18-82, diagnosis of hATTR with peripheral neuropathy (Stage 1 or 2), NIS of 10 to 130, negative pregnancy test, 2 methods of contraception Key Exclusion Criteria: AST/ALT > 1.9 x ULN, bilirubin ≥ 1.5 x ULN, platelets < 125, proteinuria, abnormal TSH levels, low vitamin A, uncontrolled HTN, HIV, HBV, HCV, Karnofsky performance status* ≤ 50, renal insufficiency, diabetes, prior liver transplant, NYHA ≥ 3, ACS, anticipated survival < 2 years, use of TTR stabilizers (tafamidis, diflunisal)	Randomized: 112 60 FAS: 106 59 PP: 83 52 Attrition: 25 (23%) 8 (13%)	Primary Endpoint: Change from baseline in mNIS+7 (least squares mean change [SE]) 1. 5.8 (1.6 to 10) 2. 25.5 (20.2 to 30.8) Difference -19.7 points; (95% CI -26.4 to -13.0) P<0.001 Improvement in mNIS+7 (<0-point increase in mNIS + 7) 1. 31 (36.5%) 2. 10 (19.2%) OR not provided P = 0.033 Secondary Endpoints: Quality of life (change from baseline in Norfolk QOL-DN questionnaire) 1 1.0 (-3.2 to 5.2) 2. 12.7 (7.4 to 17.9) LS mean difference -11.7 points; (95% CI -18.3 to -5.1) P<0.001 Improvement in Norfolk-QOL-DN ((<0-point increase): 1. 42 (50%) 2. 14 (26.9%) OR not reported P = 0.008	NA ARR 17.3%/ NNT 6 NA ARR 23.1%/ NNT 5	D/C due to AE: 1. 16 (14%) 2. 1 (1.7%) Death: 1. 5 2. 0 95% CI and p value NR for all		**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear; randomization via interactive response system; treatment concealed to all but unblinded personnel. Some differences in baseline characteristics occurred (sensorimotor and autonomic neuropathy were more severe in the inotersen group and more patients with CV symptoms in the inotersen group compared to placebo (67% vs. 55%). Performance Bias: Low; double-blinded to patient and provider, double-dummy. Detection Bias: Low; all study personnel blinded Attrition Bias: High; FAS population used for primary outcome but only included 95 inotersen patients and 56 placebo; high and unequal attrition in each group. LOCF used for missing data which could bias the results since this is a progressive disease. Reporting Bias: Unclear; pre-specified exploratory outcomes of disease progression (PND) not reported in results of trial. Other Bias: High; sponsored by Ionis Pharmaceuticals who were responsible for data analysis and writing the first draft of the manuscript. **Applicability**: Patient: Under representation of US patients and genotype most common in the US (VAL122Ile mutation). Extensive exclusion criteria also limits generalizability. Intervention: Inotersen 300 mg SQ once weekly Comparator: Placebo as comparator. No appropriate active comparator based on lack of FDA approved treatments. Outcomes: Complex outcome measures used which are difficult to interpret. Lack of clinically meaningful outcomes. Setting: 24 centers in 10 countries (US, UK, France, Italy, Germany, Portugal, Spain, Brazil, New Zealand, and Argentina). 48% from North America. Some differences in inclusion criteria by country. In Germany, Portugal and Argentina, patients had to have failed or have a contraindication to tafamidis.

Abbreviations [alphabetical order]: ACS = acute coronary syndrome; ANC = absolute neutrophil count; APAP = acetaminophen; ARR = absolute risk reduction; CI = confidence interval; DB = double-blind; FAP = familial amyloid polyneuropathy; FAS = full analysis set; ITT = intention to treat; H2 = histamine 2; hATTR = hereditary transthyretin-mediated amyloidosis; Hg = hemoglobin; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HTN = hypertension; LOCF = last observation carried forward; MC = multi-center;mITT = modified intention to treat; mNIS = modified neuropathic impairment score; N = number of subjects; NA = not applicable; NaCl = normal saline; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NYHA = New York heart association; OR = odds ratio; PC = placebo controlled; PP = per protocol; RCT = randomized controlled trial; SE = standard error; TTR = transthyretin; TSH = thyroid stimulating hormone; ULN = upper limit of normal
*Karnofsky performance status measures a patient's functional status and ranges from 0 to 100 (0=death and 100 = normal function)

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

ONPATTRO (patisiran) lipid complex injection, for intravenous use
Initial U.S. Approval: 2018

----------INDICATIONS AND USAGE----------
ONPATTRO contains a transthyretin-directed small interfering RNA and is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults. (1)

----------DOSAGE AND ADMINISTRATION----------
- For patients weighing less than 100 kg, the recommended dosage is 0.3 mg/kg every 3 weeks by intravenous infusion. For patients weighing 100 kg or more, the recommended dosage is 30 mg (2.1)
- Premedicate with a corticosteroid, acetaminophen, and antihistamines (2.2)
- Filter and dilute prior to administration (2.3)
- Infuse over approximately 80 minutes (2.4)

----------DOSAGE FORMS AND STRENGTHS----------
Lipid Complex Injection: 10 mg/5 mL (2 mg/mL) in a single-dose vial (3)

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

----------WARNINGS AND PRECAUTIONS----------
- Infusion-related reactions: Monitor for signs and symptoms during infusion. Slow or interrupt the infusion if clinically indicated. Discontinue the infusion if a serious or life-threatening infusion-related reaction occurs (5.1)
- Reduced serum vitamin A levels and recommended supplementation: Supplement with the recommended daily allowance of vitamin A. Refer to an ophthalmologist if ocular symptoms suggestive of vitamin A deficiency occur (5.2)

----------ADVERSE REACTIONS----------
The most frequently reported adverse reactions (that occurred in at least 10% of ONPATTRO-treated patients and at least 3% more frequently than on placebo) were upper respiratory tract infections and infusion-related reactions (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Alnylam Pharmaceuticals at 1-877-256-9526 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 8/2018

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

TEGSEDI (inotersen) injection, for subcutaneous use
Initial U.S. Approval: 10/2018

WARNING: THROMBOCYTOPENIA AND GLOMERULONEPHRITIS
See full prescribing information for complete boxed warning.

Thrombocytopenia
- **TEGSEDI causes reductions in platelet count that may result in sudden and unpredictable thrombocytopenia, which can be life-threatening. (5.1)**
- **Testing prior to treatment and monitoring during treatment is required (2.3, 2.4, 5.1)**

Glomerulonephritis
- **TEGSEDI can cause glomerulonephritis that may require immunosuppressive treatment and may result in dialysis-dependent renal failure. (5.2)**
- **Testing prior to treatment and monitoring during treatment is required (2.3, 2.4, 5.2)**

TEGSEDI is available only through a restricted distribution program called the TEGSEDI REMS Program (5.3).

INDICATIONS AND USAGE

TEGSEDI is a transthyretin-directed antisense oligonucleotide indicated for treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults (1).

DOSAGE AND ADMINISTRATION

- The recommended dosage is 284 mg administered by subcutaneous injection once weekly. (2.1)
- Laboratory tests must be measured prior to treatment, continue to be monitored after treatment initiation, and for 8 weeks following discontinuation of treatment, as directed. (2.3, 2.4)

DOSAGE FORMS AND STRENGTHS

Injection: 284 mg/ 1.5 mL in a single-dose prefilled syringe (3)

CONTRAINDICATIONS

- Platelet count less than 100 x 10^9/L (4, 5.1)
- History of acute glomerulonephritis caused by TEGSEDI (4, 5.2)
- Patients with a history of a hypersensitivity reaction to TEGSEDI (4, 5.7)

WARNINGS AND PRECAUTIONS

- *Stroke and Cervicocephalic Arterial Dissection:* These adverse events occurred within 2 days of first dose and with symptoms of cytokine release. Educate patients on symptoms of stroke and central nervous system arterial dissection. (5.4)
- *Inflammatory and Immune Effects*: Serious neurologic adverse reactions consistent with inflammatory and immune effects occurred. (5.5)
- *Liver Effects:* Monitor alanine amino transferase, aspartate aminotransferase, and total bilirubin every 4 months during treatment and in case of symptoms of hepatic dysfunction. (5.6)
- *Hypersensitivity Reactions:* If these occur, discontinue and initiate appropriate therapy. (5.7)
- *Uninterpretable Platelet Counts: Reaction between Antiplatelet Antibodies and ethylenediaminetetra-acetic acid*: Platelet clumping can cause uninterpretable platelet measurement; repeat test if thisis suspected. (5.8)
- *Reduced Serum Vitamin A Levels and Recommended Supplementation:* Supplement with the recommended daily allowance of vitamin A. Refer to an ophthalmologist if ocular symptoms suggestive of vitamin A deficiency occur. (5.9)

ADVERSE REACTIONS

The most common adverse reactions (those that occurred in at least 20% of TEGSEDI-treated patients and more frequently than on placebo) were injection site reactions, nausea, headache, fatigue, thrombocytopenia, and fever (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Ionis Pharmaceuticals, Inc. at 1-833-642-5232 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2018

Drugs for Hereditary Transthyretin-Mediated Amyloidosis (hATTR)

Goal(s):

- To limit utilization of medications for hATTR to FDA-approved indications.

Length of Authorization:

Up to 6 months

Requires PA: (Both pharmacy and physician-administered claims)

- All medications indicated for hATTR

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 therapies for hATTR amyloidosis

Drug	Indication
Inotersen	Polyneuropathy of hATTR
Patisiran	Polyneuropathy of hATTR
Tafamidis	Cardiomyopathy of hATTR

Approval Criteria		
1. Is this a request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code.	
3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Is this an FDA approved indication of hATTR amyloidosis supported by transthyretin mutation proven by genetic testing (See Table 1)?	**Yes**: Go to #5	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
5. Does the patient have clinical signs and symptoms of disease (peripheral/autonomic neuropathy, motor disability)?	**Yes**: Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the patient on Vitamin A supplementation?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Is the request for or is the patient on concurrent use of more than one hATTR therapy (including diflunisal)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #8
8. Has the patient had a liver transplantation?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #9
9. Was the medication prescribed or in consultation with a neurologist?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness.
10. Is the request for patisiran?	**Yes**: Approve for 6 months	**No**: Go #11
11. Is the request for inotersen?	**Yes:** Go to # 12	**No:** Go to #14
12. Has a baseline platelet count been obtained in the previous 3 months and are ≥ 125 x 10^9/L?	**Yes:** Go to #13 Document baseline platelet count:_____ Date of Lab:_____	**No:** Pass to RPh. Deny; medical appropriateness.
13. Has baseline renal function been evaluated in the previous 3 months?	**Yes:** Approve for 6 months Document baseline serum creatinine and BUN:_____ Date of Lab:_____	**No:** Pass to RPh. Deny; medical appropriateness
14. Is the request for a newly approved hATTR therapy and does the indication match the FDA approved indication?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has the patient had a documented response to treatment including at least one of the following: a. Improved neurologic impairment b. Improved motor function c. Improved quality of life	**Yes:** Go to #2	**No:** Pass to RPh; Deny (medical appropriateness)
2. Has the patient experienced stabilization OR improvement from baseline in one of the following: a. Baseline polyneuropathy disability (PND) score b. Familial amyloid polyneuropathy (FAP) stage	**Yes:** Go to #3	**No:** Pass to RPh; Deny (medical appropriateness)
3. Is the renewal for inotersen?	**Yes:** Go to #4	**No:** Approve for 12 months
4. Does the patient have a platelet count ≥ 100 X 10^9/L?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 7/19 (MH)
Implementation: TBD

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Atopic Dermatitis Class Update and Dupilumab Drug Update

Date of Review: July 2019

Date of Last Review: March 2018
End Date of Literature Search: 4/17/19

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

Purpose for Class Update: Review new evidence for drugs used to manage atopic dermatitis (AD). Evaluate evidence for expanded indications for dupilumab: treatment of moderate-to-severe AD in adolescents and add on therapy to manage moderate-to-severe asthma.

Research Questions:
1. Is there new high quality evidence demonstrating differences in efficacy or effectiveness between the different classes of drugs used to manage AD (topical corticosteroids, topical calcineurin inhibitors, crisaborole, and immunomodulators)?
2. Is there evidence demonstrating differences in harms data between the different AD therapies?
3. Are there subgroups of patients, based on demographics (e.g., age, race, sex), in which one AD medication would be more effective or associated with less harm?

Conclusions:
Atopic Dermatitis Class Update
- A good quality systematic review and meta-analysis published in 2018 sought to evaluate the overall safety and efficacy of dupilumab treatment in moderate-to-severe AD.[1] The pooled of 6 trials with a low risk of bias revealed significant improvements in Eczema Area and Severity Index (EASI) score (standard mean difference [SMD] = −0.89, 95% Confidence Interval [CI] −1.0 to −0.78), percentage of body surface area (SMD = −0.83, 95% CI −0.90 to −0.75), with dupilumab compared to placebo.[1] Dupilumab treatment was also associated with a significant increase in the proportion of patients achieving Investigator's Global Assessment (IGA) response (Relative Risk [RR] = 3.82; 95% CI 3.23 to 4.51) and a similar incidence of adverse events (RR = 1.0; 95% CI 0.96 to 1.04, p = 0.83) versus placebo.[1]
- In August 2018 the National Institute for Health and Care Excellence (NICE) published guidance for dupilumab in treating moderate-to-severe AD.[2] Dupilumab is recommended as an option for treating moderate to severe atopic dermatitis in adults, only if the disease has not responded to at least 1 other systemic therapy, such as cyclosporine, methotrexate, azathioprine and mycophenolate mofetil, or if these are contraindicated or not tolerated.[2]

New Indications for Dupilumab
- The use of dupilumab in adolescents for AD was approved by the Food and Drug Administration (FDA) March 2019.[3] The efficacy and safety of dupilumab in adolescent subjects was evaluated in a multicenter, randomized, double-blind, placebo-controlled trial in 251 adolescent subjects 12 to 17 years of age, with

moderate-to-severe AD. The primary endpoint was the proportion of subjects with an IGA 0 (clear) or 1 (almost clear) and at least a 2-point improvement on the 5 point scale from baseline to Week 16.[3] At week 16, 24% of the dupilumab subjects had an IGA of 0 or 1 versus 2% of the placebo-treated subjects (p<0.001).[3]

- In October 2018, dupilumab received an expanded FDA-approved indication as add-on maintenance therapy in adults and adolescents aged 12 years and older with moderate-to-severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma.[3] The efficacy and safety of dupilumab for treatment of asthma were evaluated in 2 randomized, double-blind, placebo-controlled, phase 3 trials.[4,5]
- In the smaller trial, 210 patients 12 years of age and older with glucocorticoid- treated severe asthma were randomized to receive add-on treatment with dupilumab 300 mg (following a loading dose of 600 mg) or placebo every 2 weeks for 24 weeks.[4] Moderate quality evidence from this small randomized clinical trial (RCT) showed the mean percentage reduction in the oral corticosteroid dose from baseline to week 24, was 70.1% with dupilumab versus 41.9% with placebo (mean difference (MD) -28.2%; 95% CI -40.7 to -15.8; p<0.001).[4]
- In a trial of 1902 subjects, dupilumab efficacy and safety were assessed in patients aged 12 years of age and older with moderate-to-severe uncontrolled asthma despite treatment with an inhaled glucocorticoid and long acting beta agonist or leukotriene receptor antagonist.[5] Moderate quality evidence from this large placebo-controlled trial showed the annualized rate of severe asthma exacerbations was reduced with dupilumab over 52 weeks. Annualized rate of asthma exacerbations was 0.46 among patients assigned to 200 mg of dupilumab every 2 weeks and 0.87 among those assigned to a matched placebo, (RR 0.52; 95% CI 0.41 to 0.66; P<0.001); similar results were seen with the dupilumab dose of 300 mg every 2 weeks.[5]
- Moderate quality evidence showed the most frequent adverse event, occurring in 5% or more of the patients and at higher rates among asthmatic patients who received dupilumab than among those who received placebo, was injection-site reaction (in 15.2% of patients who received lower-dose dupilumab vs. 5.4% of those who received matched placebo, and in 18.4% of patients who received higher-dose dupilumab vs. 10.3% of those who received matched placebo).[5]

Recommendations:

- To support administration of PA criteria, remove dupilumab from atopic dermatitis and topical antipsoriatic prior authorization (PA) criteria and create a new PA document for dupilumab utilization in moderate-to-severe asthma and moderate-to-severe AD. Update PA criteria for dupilumab based on FDA approved ages for AD and add renewal criteria.
- Reorder questions in the dupilumab PA criteria to assess the prescribing practitioner at the beginning of the PA review.
- Review costs in executive session.

Summary of Prior Reviews and Current Policy

In 2017, the Health Evidence Review Commission (HERC) modified conditions funded on line 424 (moderate/severe inflammatory skin disease) to include psoriasis, and AD.[6] Guideline Note 21 defines severe inflammatory skin disease as having 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: 1) at least 10% of body surface area involved; and/or 2) hand, foot or mucous membrane involvement.[7] Due to the prioritized list revisions, moderate to severe AD became a funded condition effective January 1, 2018. Mild AD is classified on line 544 and continues to be an unfunded condition. Oregon's legislature approved funding for lines 1-469 of the prioritized list as of January 1, 2019.[7] At the May 2018 meeting, the Pharmacy and Therapeutics (P and T) committee approved revising the PA criteria for topical antipsoriatic drugs to include agents used to manage atopic dermatitis. The recommendation to make dupilumab a non-preferred medication on the Practitioner-Managed Prescription Drug Plan (PMPDP) with PA criteria was also approved at this meeting. After reviewing comparative costs in executive session, tacrolimus 0.03%

ointment, tacrolimus 0.1% ointment, and pimecrolimus 1% cream were designated as preferred agents and crisaborole was maintained as a non-preferred agent. The PDL status for medications used to manage AD is presented in **Appendix 1**.

The comparative safety and efficacy for omalizumab, benralizumab, reslizumab, and mepolizumab for the treatment of severe asthma were reviewed at the July 2018 P and T Committee meeting. All 4 medications are non-preferred drugs on the PMPDP subject to prior authorization (PA) criteria. Omalizuamb is also indicated for management of chronic urticaria; however, this diagnosis is not funded according to the Health Evidence Review Commission (HERC) prioritized list.[7]

Background:

Atopic Dermatitis

Atopic dermatitis (AD) is chronic skin disorder characterized by pruritus and recurrent eczematous lesions accompanied by inflammation.[8] Other clinical features may include xerosis, erythema, erosions, oozing, and lichenification of the skin. The cause is unknown, but may be due to genetics or immunologic dysfunction.[9] Although it may affect all age groups, AD is most common in children. The disease affects 15-20% of children in developed countries and approximately 11% of U.S children.[10,11] Estimated prevalence of AD in U.S. adults is 3%.[10] Onset of AD is typically between the ages of 3 and 6 months, with approximately 60% of patients developing the disease during the first year of life and 90% by the age of 5 years.[12] AD can persist into adulthood in about one third of affected individuals.[10]

The mainstays of therapy for AD are skin care with frequent application of an emollient to maintain the skin's epidermal barrier, avoidance of triggers, and anti-inflammatory therapy with topical corticosteroid (TCS) or a topical calcineurin inhibitor (TCI) if needed.[9] The use of TCS and TCI therapies in AD is supported by The American College of Dermatology's 2014 guideline[13] and 2004 guidance from the National Institute for Health and Care Excellence.[14] Topical corticosteroids are recommended for AD-affected individuals who have failed to respond to good skin care and regular use of emollients alone. However, prolonged use of TCS can result in telangiectasia, increased hair, skin tears, easy bruising, poor wound healing, acne and rosacea, and thinning/atrophic skin changes, which can be permanent.[15] TCIs are considered a second-line option in both adults and children with AD who have not responded to TCS or when those treatments are not advisable.[16,17] The main rationale for TCI use is that they do not cause skin atrophy and are therefore of particular value in delicate skin areas such as the face, neck, and skin folds.[13] All topical preparations can sting, but there is evidence that this may be more problematic with TCI preparations.[13]

Patients with AD that cannot be controlled with TCS or TCI therapy can be treated with short-term phototherapy with narrow band ultraviolet B (UVB) light or systemic immunomodulators such as cyclosporine, azathioprine, mycophenolate mofetil, methotrexate, or oral corticosteroids.[13] The use of systemic immunomodulators in AD is considered off label and only oral prednisone is FDA approved to treat AD. Treatment with cyclosporine carries important risks of acute and chronic nephrotoxicity, can have hemodynamic effects that result in hypertension, and can increase the risk of infections and cancer.[13] Cyclosporine nephrotoxicity can be irreversible, and this risk increases with longer durations of treatment.[13] As a result, treatment with cyclosporine for AD is typically limited to one year. 2004 National Institute for Health and Care Excellence (NICE) Guidance recommends systemic corticosteroids, phototherapy, and systemic immunosuppressants as "treatments of last resort" in AD patients.[14] The 2014 American Academy of Dermatology guidelines reinforce the NICE recommendations for systemic immunomodulators as treatments for patients with refractory AD who fail all other therapies.[13] Two additional agents with novel mechanisms of action have recently been added to AD treatment algorithms. Crisaborole is a topical phosphodiesterase 4 (PDE4) inhibitor approved for mild-to-moderate AD in adults and children. PDE4 is a regulator of inflammation, and intracellular inflammatory cell PDE4 activity is increased in AD.[13] Crisaborole is available as an ointment that is applied twice daily. Dupilumab is an injectable monoclonal antibody that has been evaluated as a systemic therapy for moderate-to-severe AD refractory to topical treatments in adults. Clinical trials are currently underway with other biologics including ustekinumab, secukinumab, and apremilast to assess their efficacy in treating patients with AD.[8]

Clinical studies have utilized several scales for defining the severity of AD, including the Eczema Area and Severity Index (EASI) and IGA. The EASI assesses the severity of, and body surface area affected by, AD symptoms including erythema, induration/papulation/edema, excoriations, and lichenification.[12] Each symptom is graded systematically for specific anatomical regions and summarized in a composite score. EASI scores range from 0 to 72, with higher scores indicating greater severity and extent of AD.[12] An EASI score of 7.1 to 21 is classified as mild AD, an EASI score of 21.1 to 50 is considered moderate AD, and severe AD ranges from an EASI score of 50.1 to 72.[12] EASI outcomes are measured as a percentage improvement in EASI score from baseline as EASI 50, 75, or 90. IGA is a clinician-reported outcome measure that has been used to evaluate severity of AD at a given point in time.[12] This measure was used to evaluate clinical response to treatment in studies evaluating new AD therapies.[12] In these trials, a 5-point scale ranging from 0 (clear) to 4 (severe) was used to assess changes in the severity of skin lesions. In most trials, scores less than or equal to 1 were generally classified as "treatment success," whereas scores greater than 1 were considered "treatment failure."[12] The IGA does not assess disease extent as body regions are not included in the IGA scoring. One systematic review concluded that although the IGA is easy to perform, the lack of standardization precludes any meaningful comparisons between studies which impedes data synthesis to inform clinical decision making.[12] These scales are primarily used in clinical trials and rarely in clinical practice, as they were generally not designed for this purpose.[12]

Severe Asthma

Asthma is a heterogeneous disease, characterized by chronic airway inflammation.[18] According to the 2007 National Asthma Education and Prevention Program (NAEPP) guidelines, asthma severity is classified according to symptoms and level of treatment required to control exacerbations.[19] Mild asthma (step 1 or 2) is well controlled with low dose inhaled corticosteroid (ICS) therapy.[19] Moderate (Step 3), and severe (Steps 4 and 5) asthma may require more potent ICS and addition of other controller-drug treatments.[19] The 2018 Global Initiative for Asthma (GINA) guidelines recommend a biologic agent for patients with severe asthma unresponsive to controller-drug treatments.[18] Severe asthma is reported to account for about 5 to 10 percent of the total asthma population, but exact prevalence is unknown due to heterogeneity in presentation of severe asthma.[20] Although the prevalence of severe asthma is relatively low, it accounts for 50% of the health care costs associated with managing exacerbations.[21]

Recognition that asthma is not a single disease, but multiple, overlapping, phenotypes of disease has changed the way asthma is categorized and treated.[22,23] Phenotyping severe asthma based on demographic or clinical characteristics may help target treatments more effectively. Some asthma phenotypes include eosinophil predominant, neutrophil predominant, and allergic asthma.[23] Omalizumab is an anti-immunoglobulin E (IgE) monoclonal antibody that has been available for over a decade to manage severe allergic asthma and chronic urticaria. Three additional monoclonal antibodies; mepolizumab, reslizumab, and benralizumab, mediate the effects of interleukin (IL)-5 and are effective in management of eosinophilic asthma as add on therapy. Activated eosinophils can increase airway smooth muscle contraction and mucous secretion. The monoclonal antibodies that mediate IL-5 activity are FDA-approved to treat severe asthma in patients with an eosinophilic phenotype of asthma. Safety and efficacy of these agents have not been assessed in head-to-head trials. Several monoclonal antibodies targeting different cytokines (IL-4 and IL-13) are currently being investigated for their safety and efficacy in treating severe asthma. Dupilumab, an IL-4 receptor antagonist, recently received an expanded indication as add on maintenance therapy for moderate to severe asthma.[3]

Although the biologic agents used to manage severe asthma are well-tolerated, serious adverse reactions have been reported. Anaphylaxis has been reported in 0.3% of patients receiving reslizumab, so the drug carries an FDA boxed warning recommending observation after infusion.[24] Hypersensitivity reactions have been observed with mepolizumab and benralizumab; however neither drug has a boxed warning regarding anaphylaxis.[25,26] There is insufficient evidence on the long-term safety and effectiveness of monoclonal antibodies used to manage severe asthma as the length of follow-up in some of the randomized trials with the biologic agents was only 24 weeks, and no trial was longer than 15 months.

There are notable differences between each biologic agent approved to treat asthma primarily related to the age of administration, route of administration, dosing regimen, and FDA-approved indication. Currently, 4 of the monoclonal antibodies used to manage asthma (benralizumab, reslizumab, mepolizumab, and omalizumab) must be administered by a health care provider. Dupilumab is the only monoclonal antibody approved for self-administration.[3] **Table 1** summarizes significant prescribing information for the 5 biologic agents with FDA approval to treat severe asthma.

Table 1. Monoclonal Antibodies Approved to Manage Severe Asthma [3,24-27]

Generic Name	Brand Name	FDA Approval Year	Target	FDA Approved Indication	Maintenance Dose and Administration Route	FDA Approved Administration Age	FDA Boxed Warning	Blood Eosinophil Levels in Clinical Trials in Primary Analysis Population
Dupilumab	Dupixent®	2018	IL-4 Receptor	-Moderate to severe atopic dermatitis -Add on maintenance treatment for moderate to severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma	Atopic Dermatitis: 1. Adults: 300 mg SC every 2 weeks 2. Adolescents: < 60 kg: 200 mg SC every 2 weeks ≥60 kg: 300 mg SC every 2 weeks -Asthma: Adults and Adolescents: 200 to 300mg SC every 2 weeks	Atopic Dermatitis: ≥ 12 yo Moderate to Severe Asthma: ≥ 12 yo	No	Subjects enrolled in clinical trials without requiring a minimum baseline blood eosinophil count
Benralizumab	Fasenra™	2017	IL-5 Receptor	Severe asthma with an eosinophilic phenotype	30 mg SC every 8 weeks	≥ 12 yo	No	≥300 cells/µL
Reslizumab	Cinqair®	2016	IL-5	Severe asthma with an eosinophilic phenotype	3 mg/kg IV infusion every 4 weeks	≥ 18 yo	Yes: for possible anaphylaxis	≥ 400 cells/µL
Mepolizumab	Nucala®	2015	IL-5	-Severe asthma with an eosinophilic phenotype -EGPA in adults	-Asthma: 100 mg SC every 4 weeks -EGPA: 300 mg SC every 4 weeks	-Asthma: ≥ 12 yo -EGPA: ≥ 18 yo	No	≥ 150 cells/µL at screening or ≥ 300 cells/µL in the previous year
Omalizumab	Xolair®	2003	IgE	-Moderate to severe persistent asthma -Antihistamine refractory CSU	-Asthma: 75 to 375 mg SC every 2 to 4 weeks. (Dosing is determined by weight and serum IgE levels for asthma) -CSU: 150 to 300 mg SC every 4 weeks	-Asthma: ≥ 6 yo -CSU: ≥ 12 yo	Yes: for possible anaphylaxis	Not Applicable

Abbreviations: CSU = Chronic Spontaneous Urticaria; EGPA = Eosinophilic Granulomatosis with Polyangiitis; FDA = Food and Drug Administration; IgE = immunoglobulin E; IL-5 = interleukin-5; IV = intravenous; SC = subcutaneous; YO = years old

Clinically relevant outcomes to assess treatments of severe asthma include reduction in asthma exacerbations that result in: 1) decreased Emergency Department (ED) visits or hospitalizations; 2) decreased chronic use of oral corticosteroids; 3) improved quality of life; and 4) improved symptom management. Three instruments are commonly used in clinical trials to assess quality-of-life and symptom management related to asthma. These tests are self-administered and subject to recall bias but have been validated with highly consistent reproducibility between users. The Asthma Control Questionnaire (ACQ) is a 5-item

questionnaire that assesses asthma symptoms and rescue inhaler use in the preceding week.[28] Scores range from 0 (totally controlled) to 6 (severely uncontrolled), with a change in score of 0.5 units the minimally clinical important difference.[29] An ACQ score consistently greater than 1.5 indicates poor symptom control.[29] Change from baseline in forced expiratory volume in 1 second (FEV1) is a common surrogate endpoint used in asthma treatment trials since it is highly reproducible. Minimally important values from research in COPD patients suggest minimally important FEV1 changes range from 100-140 ml.[30]

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

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

New Systematic Reviews:
Safety and efficacy of Dupilumab
A good quality systematic review and meta-analysis published in 2018 evaluated the overall safety and efficacy of dupilumab treatment in moderate-to-severe atopic dermatitis.[1] Six trials with a low risk of bias involving 2447 patients met inclusion criteria.[1] However, all the included trials were funded by the manufacturer (Sanofi and Regeneron Pharmaceuticals).[1] Duration of treatment ranged from 4 to 52 weeks and dupilumab was administered via the subcutaneous route in doses ranging from 300 mg once weekly to 300 mg biweekly.[1] In 4 trials dupilumab was analyzed as monotherapy, while in the other 2 trials dupilumab was administered in combination with topical corticosteriods.[1]

The meta-analysis revealed significant improvements in EASI score with moderate heterogeneity (SMD = −0.89, 95% CI −1.0 to −0.78; P<0.001; I^2=45%) and percentage of body surface area with minimal heterogeneity (SMD = −0.83, 95% CI −0.90 to −0.75; P<0.001; I^2=9%) with both doses of dupilumab compared to placebo.[1] A standardized mean difference greater than 0.8 represents a clinically significant improvement in AD symptoms. Subgroup analysis showed that the 300 mg once weekly dosage seemed more effective than the every 2 week dosage in reduction of EASI (-0.93 vs −0.86), however, there was significant heterogeneity in 300 mg once weekly group (I^2 = 55%, p=0.05).[1] There was a high level of heterogeneity with the pooled analysis of puritis NRS scores and quality of life (DLQI) scores.[1] Dupilumab treatment was also associated with a significant increase in the proportion of patients achieving IGA response with minimal heterogeneity (RR = 3.82; 95% CI 3.23 to 4.51; p<0.001; I^2=16%) and a similar incidence of adverse events with minimal heterogeneity (RR = 1.0; 95% CI 0.96 to 1.04, p=0.83; I^2=11%) versus placebo.[1] The most frequently reported adverse events included nasopharyngitis, exacerbation of AD, headache and upper respiratory infection.[1] This analysis provides evidence that dupilumab results in clinically relevant improvements in signs and symptoms of AD.[1] However, more trials are needed to further investigate the long-term efficacy and safety of dupilumab in moderate-to-severe AD. Both dose regimens of dupilumab seemed to have similar benefits in ameliorating signs and symptoms of AD.[1] The FDA-approved dose of dupilumab for AD in adults is 300 mg subcutaneously given every other week after an initial 600 mg dose.[3]

After review, 2 systematic review was 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).[31,32]

New Guidelines:

High Quality Guidelines:

National Institute for Health and Care Excellence

In August 2018 the National Institute for Health and Care Excellence (NICE) published guidance for dupilumab in treating moderate-to-severe AD.[2] Recommendations include:

1. Dupilumab is recommended as an option for treating moderate to severe atopic dermatitis in adults, only if:
    - the disease has not responded to at least 1 other systemic therapy, such as cyclosporine, methotrexate, azathioprine and mycophenolate mofetil, or these are contraindicated or not tolerated.[2]
2. Stop dupilumab at 16 weeks if the atopic dermatitis has not responded adequately. An adequate response was defined as:
    - at least a 50% reduction in the Eczema Area and Severity Index score (EASI 50) from when treatment started and
    - at least a 4‑point reduction in the Dermatology Life Quality Index (DLQI) from when treatment started.

After review, 2 guidelines were excluded due to poor quality.[33,34]

New Indications

Dupilumab approved for use in adolescents with atopic dermatitis

The use of dupilumab in adolescents for AD was approved by the FDA March 2019.[3] When originally approved for adults, dupilumab was only available as a 300 mg/2 ml prefilled syringe. With the expanded indication for use in patients 12 years and older, dupilumab is presently available in a 200 mg/1.4 ml pre-filled syringe. The efficacy and safety of dupilumab in adolescent subjects was evaluated in a multicenter, randomized, double-blind, placebo-controlled trial in 251 subjects 12 to 17 years of age, with moderate-to-severe AD defined by an IGA score ≥3 (scale of 0 to 4), an EASI score ≥16 (scale of 0 to 72), and a minimum body surface area (BSA) involvement of ≥10%.[3] Eligible subjects enrolled into this trial had previous inadequate response to topical medication.[3] Patients were randomized into one of three treatment groups for the controlled period of 16 weeks: the first group was treated with dupilumab subcutaneous injection 200 mg or 300 mg every two weeks, based on weight (with an initial dose of 400 mg or 600 mg respectively). The second group was treated with 300 mg dupilumab every four weeks (with an initial dose of 600 mg), and the third group was treated with placebo every two weeks. The primary endpoint was the proportion of subjects with an IGA 0 (clear) or 1 (almost clear) and at least a 2-point improvement from baseline to Week 16.[3] At week 16, 24% of the dupilumab subjects had an IGA of 0 or 1 versus 2% of the placebo-treated subjects ($p<0.001$).[3] The safety profile of dupilumab in these subjects through week 16 was similar to the safety profile from studies in adults with atopic dermatitis.[3]

Dupilumab approved as add on therapy for asthma

In October 2018, dupilumab received an expanded FDA-approved indication as add-on maintenance therapy in adults and adolescents aged 12 years and older with moderate-to-severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma.[3] The efficacy and safety of dupilumab were evaluated in 2 randomized, double-blind, placebo-controlled, phase 3 trials.[4,5] In the smaller trial, 210 patients 12 years of age and older with glucocorticoid-treated severe asthma were randomized to receive add-on treatment with dupilumab 300 mg (following a loading dose of 600 mg) or placebo every 2 weeks for 24 weeks.[4] Subjects were also receiving inhaled corticosteroids and 2 additional asthma controller medications. The primary end point was the percentage reduction in the glucocorticoid dose at week 24. Oral corticosteroid doses were reduced every 4 weeks from week 4 to week 20 as long as asthma control was

maintained.[4] Moderate quality evidence shows the mean percentage reduction in the oral corticosteroid dose from baseline to week 24, was 70.1% with dupilumab versus 41.9% with placebo (mean difference (MD) -28.2%; 95% CI -40.7 to -15.8; p<0.001).[4] At week 24, 52% of patients in the active treatment group had completely discontinued oral corticosteroids, compared to 29% of those in the placebo group (OR 2.74; p=0.002).[4] Use of dupilumab also decreased severe asthma exacerbations (annualized rate 0.65 for dupilumab vs. 1.60 for placebo; RR 0.41; 95% CI 0.26 to 0.63) and improved lung function (FEV1) was 0.22 liters higher; 95% CI 0.09 to 0.34) compared to placebo.[4] The benefits were greatest in patients with higher baseline blood eosinophil counts.[4] Injection-site reactions were more common with dupilumab than with placebo (9% vs. 4%).[4] Transient blood eosinophilia was observed in more patients in the dupilumab group than in the placebo group (14% vs. 1%).[4] In patients with glucocorticoid-dependent severe asthma, dupilumab treatment reduced oral glucocorticoid use while decreasing the rate of severe exacerbations and increasing the FEV1.[4]

In a trial of 1902 subjects, dupilumab efficacy and safety were assessed in patients aged 12 years of age and older with moderate-to-severe uncontrolled asthma despite treatment with an inhaled glucocorticoid and long acting beta agonist or leukotriene receptor antagonist.[5] Patients were randomized in a 2:2:1:1 ratio to receive add-on subcutaneous dupilumab at a dose of 200 or 300 mg every 2 weeks or matched-volume placebos for 52 weeks.[5] The primary end points were the annualized rate of severe asthma exacerbations and the absolute change from baseline to week 12 in the FEV1 before bronchodilator use in the trial population.[5] Change from baseline in forced expiratory volume in 1 second (FEV1) is a common surrogate endpoint used in asthma treatment trials. Research in COPD patients suggest minimal clinically important FEV1 changes range from 100-140 ml.[30] Moderate quality evidence from this trial showed the annualized rate of severe asthma exacerbations was reduced with dupilumab compared to placebo over 52 weeks. Annualized rate of asthma exacerbations was 0.46 among patients assigned to 200 mg of dupilumab every 2 weeks and 0.87 among those assigned to a matched placebo, (RR 0.52; 95% CI 0.41 to 0.66; P<0.001); similar results were seen with the dupilumab dose of 300 mg every 2 weeks (0.52 with dupilumab vs. 0.97 with placebo; RR 0.54; 95% CI 0.43 to 0.68; P<0.001).[5] At week 12, the FEV_1 had increased by 0.32 liters in patients assigned to the lower dose of dupilumab (difference vs. matched placebo, 0.14 liters; P<0.001); similar results were seen with the higher dose.[5] The most frequent adverse event, occurring in 5% or more of the patients and at higher rates among patients who received dupilumab than among those who received placebo, was injection-site reaction (in 15.2% of patients who received lower-dose dupilumab vs. 5.4% of those who received matched placebo, and in 18.4% of patients who received higher-dose dupilumab vs. 10.3% of those who received matched placebo).[5] More details about the 2 trials are outlined in **Table 2.**

How dupilumab compares to the other monoclonal antibodies that are approved for treatment of eosinophilic asthma (i.e.; benralizumab, mepolizumab, and reslizumab) remains to be determined, and there is insufficient data to evaluate long-term safety of dupilumab.

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

Table 2. Comparative Evidence Table: Dupilumab in Severe Asthma

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Rabe, et al.[4] VENTURE DB, PC,MC, RCT N = 210	1. Dupilumab 600 mg SC loading dose x 1 dose followed by 300 mg SC every 2 weeks for 24 weeks. 2. Placebo SC every 2 weeks for 24 weeks	Demographics: 1. Mean age: 51 yo 2. Female Gender: 60% 3. Former Smoker: 20% 4. Number of severe asthma exacerbations in the year prior: 2 5. Mean blood eosinophil count: 350 cells/µL 6. ACQ-5 score: 2.5 7. Blood eosinophils ≥ 300 cell/µL: 47% (dupilumab); 38% (placebo) 8. Mean oral glucocorticoid dose: prednisone 11 mg Key Inclusion Criteria: 1. Patients 12 yo or older with asthma for ≥ 1 year receiving systemic glucocorticoids in the previous 6 months. 2. During the 4 weeks before screening treatment had to include high dose inhaled glucocorticoid and 2 controllers (LABA or LRA for at least 3 months. 3.FEV1 ≤ 80% Key Exclusion Criteria: 1. Weight less than 30 kg 2. COPD or other lung disease that impairs lung function 3. Current smoker 4. Previous smoker with smoking history > 10 pack years	ITT: 1. 103 2. 107 PP: 1. 101 2. 102 Attrition: 1. 2 (2%) 2. 5 (5%)	Primary Endpoint: Percentage reduction in oral glucocorticoid dose from baseline to week 24. 1. -70.1 ± 4.9% 2. -41.9 ± 4.6% MD -28.2 (95% CI -40.7 to -15.8) P<0.001 Secondary Endpoint: 1. Proportion of patients with reduction of at least 50% of oral glucocorticoid at week 24 1. 82 (79.6%) 2. 57 (53.3)% OR 3.98 (95% CI 2.06 to 7.67) P<0.001 2. Proportion of patients with a reduction in oral glucocorticoid to < 5 mg per day at week 24 1. 74 (71.8%) 2. 40 (37.4%) OR 4.48 (95% CI 2.39 to 8.39) P<0.001	NA 26.3%/4 34.4%/3	AEs 1. 64 (62%) 2. 69 (64%) SAEs 1. 9 (9%) 2. 6 (6%) AE leading to drug discontinuation 1. 1 (1%) 2. 4 (4%) P value and 95% CI NR for all	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomly assigned in a 1:1 ratio via IVRS. Stratified according to oral glucocorticoid dose (≤10 mg per day vs. > 10 mg per day prednisone or prednisolone). Performance Bias: Low. Dupilumab and placebo provided in identically matched 2 mL prefilled syringes Detection Bias: Both the patient and the Investigator blinded to treatment assignment. Attrition Bias: Low. Low rate of attrition. Reporting Bias: Low. Protocol available online. Other Bias: Unclear. Protocol developed by Sanofi and Regeneron. Several authors report receiving grants from Regeneron and Sanofi. **Applicability**: Patient: Patients with glucocorticoid dependent severe asthma were the primary subjects. Blood eosinophils counts were not part of the inclusion criteria. Intervention: Dupilumab doses studied in Phase 2 trial. Comparator: Placebo: head to head trial with another biologic agent would be more meaningful. Outcomes: Duration of trial was 24 weeks: relatively short time to assess safety. Primary outcome was reduction in oral steroid use, which was also substantial in the placebo arm. Reduction in severe asthma exacerbations was a secondary endpoint, but would have been a preferred primary outcome. Setting: Percentage of subjects enrolled in each geographic area is unclear. 1.East Europe: Hungary, Poland, Romania, Russia, Ukraine 2.Latin America: Argentina, Brazil, Chile, Colombia, Mexico 3.Western Countries: Belgium, Canada, Israel, Italy, Netherlands, Spain, US

2. Castro, et al.[5] QUEST DB, PC, MC, PG, RCT N=1902	1. Dupilumab 600 mg x 1 dose followed by 300 mg SC every 2 weeks over 52 weeks 2. Dupilumab 400mg x 1 dose followed by 200 mg SC every 2 weeks over 52 weeks 3. Placebo loading dose followed by matched 2ml placebo SQ every 2 weeks over 52 weeks 4. Placebo loading dose followed by matched 1.14 ml placebo SC every 2 weeks over 52 weeks	<u>Demographics</u>: 1. Mean age: 48 yo 2. Female Gender: 63% 3. Former Smoker: 19% 4. Number of severe asthma exacerbations in the previous year: 2 5. Mean blood eosinophil count: 360 cells/µL 6. Mean ACQ-5 score: 2.76 7.Blood eosinophil count ≥ 300 cells/ µL: 47% <u>Key Inclusion Criteria</u>: 1. Patients ≥12 yo with uncontrolled moderate-to-severe asthma 2. Use of inhaled glucocorticoids plus up to two additional controllers (e.g. LABA, LRA) 3. FEV1 < 80% of predicted normal 4. ACQ-5 score ≥1.5 5.Experienced either: a. treatment with systemic steroid in the past year b. hospitalization or ED medical care for asthma <u>Key Exclusion Criteria</u>: 1. Weight less than 30 kg 2. COPD or other lung disease that impairs lung function 3. Current smoker 4. Previous smoker with smoking history > 10 pack years.	<u>ITT</u>: 1. 633 2. 631 3. 321 4. 317 <u>PP</u>: 1. 469 2. 487 3. 248 4 .230 <u>Attrition</u>: 1. 164 (26%) 2. 144 (23%) 3. 73 (23%) 4. 87 (27%)	<u>Primary Endpoint</u>: .Annualized rate of severe asthma exacerbations over 52 weeks 1. 0.52 2. 0.46 3. 0.97 4. 0.87 1 vs. 3 RR 0.54 (95% CI 0.43 to 0.68) P<0.001 2 vs. 4 RR 0.52 (95% CI 0.41 to 0.66) P<0.001 2.Absolute increase from baseline in pre-bronchodilator FEV_1 at week 12 1. 0.34 L 2. 0.32 L 3. 0.21 L 4. 0.18 L 1 vs. 3 MD 0.13 (95% CI 0.08 to 0.18) P<0.001 2 vs. 4 MD 0.14 (95% CI 0.08 to 0.19 P<0.001 <u>Secondary Endpoints</u>: 1.Percent increase from baseline in pre-bronchodilator FEV_1 at week 12 1. 23.1% 2. 21.3% 3. 13.7% 4. 12.1% 1 vs. 3 MD 9.4% (95% CI 5.74 to 13.07) P<0.001 2 vs. 4 MD 9.2% (95% CI 5.54 to 12.92) NS	NA NA NA NA NA NA	<u>AEs</u> 1. 515 (82%) 2. 508 (81%) 3. 270 (8.4%) 4. 257 (82%) <u>SAEs</u> 1. 55 (8.7%) 2. 49 (7.8%) 3. 27 (8.4%) 4.26 (8.3%) <u>AE leading to drug discontinuation</u> 1. 44 (7.0%) 2. 19 (3.0%) 3. 10 (3.1%) 4. 19 (6.1%) <u>Death</u> 1. 4 (0.6%) 2. 1 (0.2%) 3. 0 (0%) 4. 3(1%) P value and 95% CI NR for all	NA	**Risk of Bias (low/high/unclear)**: <u>Selection Bias</u>: Low. Randomized 2:2:1:1 via IVRS at a centralized treatment allocation system. Stratified by age (< 18 yo, 18-64 yo, ≥65 yo) and eosinophil count (≤150 cells/µL, 150-299 cells/µL, ≥ 300 cells/µL) at screening. Baseline demographics were similar across treatment arms. <u>Performance Bias</u>: Low. Placebo matched in similar volume to 200 or 300 mg dupilumab dose in identically matched glass pre-filled syringes. <u>Detection Bias</u>: Unclear. Patients and investigators blinded to assigned drug or placebo, but not the dose level of placebo/dupilumab. Injection site reactions with the active drug may have resulted in unblinding of treatment assignment. <u>Attrition Bias</u>: High. Attrition rates were greater than 20% in all arms. More patients in the 300mg dupilumab arm dropped out due to adverse effects compared to the 200mg arm (7% vs. 3%). <u>Reporting Bias</u>: Low. Protocol available on-line. <u>Other Bias:</u> Unclear. Protocol developed by Sanofi and Regeneron. Data collected by investigators and analyzed by sponsors. Several authors report receiving grants from Regeneron and Sanofi. **Applicability**: <u>Patient</u>: Results apply to patients with uncontrolled moderate-to-severe asthma on multiple therapies. Blood eosinophils counts were not part of the inclusion criteria <u>Intervention</u>: Dupilumab doses studied in Phase 2 trial. <u>Comparator</u>: Placebo: head to head trial with another biologic agent would be more meaningful. <u>Outcomes</u>: Reduction in rate of asthma exacerbations is a relevant primary endpoint. <u>Setting</u>: International study. Percentage of subjects enrolled in each geographic area is unclear.

Abbreviations [alphabetical order]: ACQ-5: 5-item Asthma Control Questionnaire; ARR = absolute risk reduction; CI = confidence interval; DB = double blind; FEV_1 = forced expiratory volume in 1 second; ITT = intention to treat; IVRS = interactive voice response system; mITT = modified intention to treat; LABA = long acting beta2 agonist; L = liters; LRA = leukotriene receptor antagonist; MC = multi-center; ml = milliliter; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; OR = odds ratio; PC = placebo controlled; PG = parallel group; PP = per protocol; RCT = randomized clinical trial; SC = subcutaneous

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Appendix 1: Current Preferred Drug List for Atopic Dermatitis and Miscellaneous Asthma Drugs

Generic	Brand	Form	PDL
tacrolimus	PROTOPIC	OINT. (G)	Y
tacrolimus	TACROLIMUS	OINT. (G)	Y
pimecrolimus	ELIDEL	CREAM (G)	Y
pimecrolimus	PIMECROLIMUS	CREAM (G)	Y
crisaborole	EUCRISA	OINT. (G)	N
dupilumab	DUPIXENT	SYRINGE	N

Generic	Brand	Form	PDL
montelukast	SINGULAIR	TAB CHEW	Y
montelukast	MONTELUKAST	TAB CHEW	Y
montelukast	MONTELUKAST	TABLET	Y
montelukast	SINGULAIR	TABLET	Y
benralizumab	FASENRA	SYRINGE	N
mepolizumab	NUCALA	VIAL	N
montelukast	MONTELUKAST	GRAN PACK	N
montelukast	SINGULAIR	GRAN PACK	N
omalizumab	XOLAIR	SYRINGE	N
omalizumab	XOLAIR	VIAL	N
reslizumab	CINQAIR	VIAL	N
roflumilast	DALIRESP	TABLET	N
zafirlukast	ACCOLATE	TABLET	N
zafirlukast	ZAFIRLUKAST	TABLET	N
zileuton	ZYFLO	TABLET	N
zileuton	ZILEUTON ER	TBMP 12HR	N
zileuton	ZYFLO CR	TBMP 12HR	N

Appendix 2: New Comparative Clinical Trials

A total of 15 citations were manually reviewed from the initial literature search. After further review, 14 citations were excluded because of wrong study design (eg, observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining trial is summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Blauvelt A, et al.[35] Phase 2, DB, MC, PC, PG, RCT	Dupilumab 300 mg once a week for 16 weeks Vs. Placebo And Single dose of Tdap and quadrivalent meningococcal polysaccharide vaccine at week 12	Patients aged 18-64 yo with moderate-to-severe AD for ≥ 3 yrs, with inadequate response to topical therapy, EASI ≥ 16, IGA ≥ 3, and BSA ≥ 10% N=178	Proportion of patients achieving satisfactory IgG response to tetanus toxoid at week 16	Similar positive immune responses (≥4-fold increase in antibody titer, or an antibody titer of ≥8) were achieved in the dupilumab and placebo groups to tetanus (83.3% and 83.7%, respectively; 90% CI difference -9.41 to 8.69) and meningococcal polysaccharide (86.7% and 87.0%, respectively; 90% CI difference -4.29 to 6.27). Vaccination after 12-week dupilumab therapy was not associated with adverse clinical effects
Abbreviations: AD = atopic dermatitis; BSA = Body Surface Area; CI = confidence interval; DB = double blind, EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; MC= multi-center; PC = placebo control; PG = parallel group; RCT = randomized clinical trial; Tdap – Tetanus, Diphtheria, Pertussis vaccine; YO = years old; YRS = years				

Appendix 3: Abstracts of Comparative Clinical Trials

Dupilumab does not affect correlates of vaccine-induced immunity: A randomized, placebo-controlled trial in adults with moderate-to-severe atopic dermatitis.

Blauvelt A1, Simpson EL2, Tyring SK3, Purcell LA4, Shumel B4, Petro CD4, Akinlade B4, Gadkari A4, Eckert L5, Graham NMH4, Pirozzi G6, Evans R4.

BACKGROUND: The impact of dupilumab, an anti-interleukin (IL) 4 receptor α antibody that inhibits IL-4 and IL-13 signaling, on vaccine responses of patients with atopic dermatitis (AD) is unknown.

OBJECTIVES: To assess T-cell-dependent and T-cell-independent humoral immune responses to tetanus and meningococcal vaccines, IgE seroconversion to tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccination, and dupilumab efficacy and safety.

METHODS: In a randomized, double-blinded, placebo-controlled study (NCT02210780), adults with moderate-to-severe AD received dupilumab (300 mg) or placebo weekly for 16 weeks, and single doses of Tdap and quadrivalent meningococcal polysaccharide vaccines at week 12. Primary endpoint was proportion of patients achieving satisfactory IgG response to tetanus toxoid at week 16.

RESULTS: In total, 178 patients completed the study. Similar positive immune responses (≥4-fold increase in antibody titer, or an antibody titer of ≥8) were achieved in the dupilumab and placebo groups to tetanus (83.3% and 83.7%, respectively) and meningococcal polysaccharide (86.7% and 87.0%, respectively). Dupilumab significantly decreased total serum IgE; most dupilumab-treated patients were Tdap-IgE seronegative at week 32 (62.2% dupilumab and 34.8% placebo). Dupilumab improved key AD efficacy endpoints ($P < .001$). Injection-site reactions and conjunctivitis were more common with dupilumab; AD exacerbations more frequent with placebo.

LIMITATION: Patients' prior vaccination status was not available before enrollment.

CONCLUSION: Dupilumab did not affect responses to the vaccines studied, significantly decreased IgE, and improved measures of AD severity versus placebo, with an acceptable safety profile.

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to April Week 2 2019, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to April 17, 2019

1. Dermatitis, Atopic/	12649
2. Eczema/	3458
3. Calcineurin Inhibitors/	3506
4. Pimecrolimus.mp.	862
5. Tacrolimus/	12888
6. Crisaborole.mp.	53
7. Dupilumab.mp.	250
8. 1 or 2	15591
9. 3 or 4 or 5 or 6 or 7	15533
10. 8 and 9	898
11. limit 10 to (english language and humans and yr="2018 -Current" and (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review"))	15

Atopic Dermatitis and Topical Antipsoriatics

Goal(s):

Restrict dermatological drugs only for funded OHP diagnoses. Moderate/severe psoriasis and moderate/severe atopic dermatitis treatments are funded on the OHP. Treatments for mild psoriasis, seborrheic dermatitis, keratoderma and other hypertrophic and atrophic conditions of skin are not funded.

Length of Authorization:

- From 6 to 12 months

Requires PA:

Non-preferred antipsoriatics
All atopic dermatitis drugs
STC = 92 and HIC = L1A, L5F, L9D, T0A
This PA does not apply to biologics for psoriasis, which is subject to separate clinical PA criteria.

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD 10 code.	
2. Is the diagnosis for seborrheic dermatitis, keratoderma or other hypertrophic and atrophic conditions of skin?	**Yes:** Pass to RPh; deny, not funded by the OHP.	**No:** Go to #3
3. Is the diagnosis psoriasis?	**Yes:** Go to #4	**No:** Go to #7

Approval Criteria		
4. Is the Psoriasis Moderate/Severe? Moderate/Severe psoriasis is defined as:[1] • Having 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 of the following: 1. At least 10% body surface area involved or with functional impairment and/or: 2. Hand, foot or mucous membrane involvement	**Yes:** Go to #5	**No:** Pass to RPh; deny, not funded by the OHP.
5. Is the product requested preferred?	**Yes:** Approve for length of treatment; maximum 1 year.	**No:** Go to #6
6. Will the prescriber consider a change to a preferred product? **Message:** Preferred products are evidence-based reviewed for comparative effectiveness & safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform provider of preferred alternatives. Approve for length of treatment; maximum 1 year.	**No**: Approve for length of treatment; maximum 1 year.
7. Is the diagnosis atopic dermatitis?	**Yes:** Go to #8	**No:** Go to #12

Approval Criteria		
8. Is the diagnosis Moderate/Severe Atopic Dermatitis (AD)? Moderate/Severe psoriasis is defined as:[1] • Having 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 of the following: 1. At least 10% body surface area involved or with functional impairment and/or: 2. Hand, foot or mucous membrane involvement	**Yes:** Go to #9	**No:** Pass to RPh. Deny; not funded by the OHP.
9. What is the age of the patient?	**Age less than 2 years**: Pass to RPh. Deny; medical appropriateness.	**Ages 2 years and older:** Go to #10
10. Does the patient meet the age requirements per the FDA label? • Tacrolimus 0.1% ointment is FDA approved for patients 16 years of age and older. • Tacrolimus 0.03% ointment, pimecrolimus 1% cream, and crisaborole ointment are FDA approved for patients 2 years of age and older.	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
11. Does the patient have a documented contraindication, intolerance or failed trials of at least 2 first line agents indicated for the treatment of moderate to severe AD (topical corticosteroids)?* *Note pimecrolimus and crisaborole are FDA approved to manage mild to moderate AD, while tacrolimus is FDA approved to manage moderate to severe AD.	**Yes:** Document drug and dates trialed, and intolerances (if applicable): 1._____(dates) 2._____(dates) Approve for length of treatment; maximum 6 months.	**No:** Pass to RPh. Deny; medical appropriateness
~~12. Is the drug dupilumab?~~	~~**Yes:** Go to #14~~	~~**No:** Go to #17~~
~~13. What is the age of the patient?~~ ~~• Dupilumab injection is FDA approved for patients 18 years of age and older~~	~~**Age 17 years or younger**: Pass to RPh. Deny; medical appropriateness.~~	~~**Ages 18 years and older:** Go to #15~~
12. RPH only: All other indications need to be evaluated as to whether they are funded by the OHP.*	**If funded, or clinic provides supporting literature:** Approve for 1 year.	**If not funded:** Deny, not funded by the OHP.

Approval Criteria		
14. Does the patient have a documented contraindication or failed trial of the following treatments: • Moderate to high potency topical corticosteroid (e.g., clobetasol, desoximetasone, desonide,mometasone, betamethasone, halobetasol, fluticasone, or fluocinonide) AND • Topical calcineurin inhibitor (tacrolimus, pimecrolimus) or topical phosphodiesterase (PDE)-4 inhibitor (crisaborole) AND • Oral immunomodulator therapy (cyclosporine, methotrexate, azathioprine, mycophenolate mofetil, or oral corticosteroids)?	**Yes**: Document drug and dates trialed and intolerances (if applicable): 1._____(dates) 2._____(dates) 3._____(dates) Approve for length of treatment; maximum 6 months.	**No**: Pass to RPh. Deny; medical appropriateness
13. RPH only: All other indications need to be evaluated as to whether they are funded by the OHP.*	**If funded, or clinic provides supporting literature:** Approve for length of treatment.	**If not funded:** Deny, not funded by the OHP.

P&T/DUR Review: *7/19 (DM); 5/19 (DM) 3/18 (DM); 9/17; 7/15; 1/15; 09/10; 9/09; 3/09; 5/07; 2/06*
Implementation: *TBD; 4/16/18; 10/15; 8/15; 9/13; 6/12; 9/10; 1/10; 7/09; 6/07; 9/06*

**The Health Evidence Review Commission has stipulated via Guideline Note 21 that mild, uncomplicated inflammatory skin conditions including psoriasis, atopic dermatitis, lichen planus, Darier disease, pityriasis rubra pilaris, and discoid lupus are not funded. Uncomplicated is defined as no functional impairment; and/or involving less than 10% of body surface area and no involvement of the hand, foot, or mucous membranes.*

References:

1. Oregon Health Evidence Review Commission. Coverage Guidance and Reports. http://www.oregon.gov/oha/hpa/csi-herc/pages/index.aspx Accessed May 3, 2019.

Dupilumab

Goal(s):

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

Length of Authorization:

- 6 months

Requires PA:

- Dupilumab (Dupixent)

Covered Alternatives:

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

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

Approval Criteria		
5. Will the prescriber consider a change to a preferred product? **Message:** Preferred products are evidence-based reviewed for comparative effectiveness & safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform provider of preferred alternatives. Approve for length of treatment; maximum 1 year.	**No**: Go to # 6
6. Is the medication being prescribed by or in consultation with a dermatologist or allergist who specializes in management of severe asthma?	**Yes:** Go to # 7	**No:** Pass to RPh. Deny; medical appropriateness
7. What is the age of the patient? • Dupilumab injection is FDA approved for patients 12 years of age and older	**Age 11 years or younger**: Pass to RPh. Deny; medical appropriateness.	**Ages 12 years and older:** Go to #8
8. Is the diagnosis Moderate/Severe Atopic Dermatitis (AD)? Moderate/Severe psoriasis is defined as:[1] • Having 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 of the following: 1. At least 10% body surface area involved or with functional impairment and/or: 2. Hand, foot or mucous membrane involvement	**Yes:** Go to #9	**No:** Go to #10

Approval Criteria		
9. Does the patient have a documented contraindication or failed trial of the following treatments: • Moderate to high potency topical corticosteroid (e.g., clobetasol, desoximetasone, desonide,mometasone, betamethasone, halobetasol, fluticasone, or fluocinonide) AND • Topical calcineurin inhibitor (tacrolimus, pimecrolimus) or topical phosphodiesterase (PDE)-4 inhibitor (crisaborole) AND • Oral immunomodulator therapy (cyclosporine, methotrexate, azathioprine, mycophenolate mofetil, or oral corticosteroids)?	**Yes**: Document drug and dates trialed and intolerances (if applicable): 1._____(dates) 2._____(dates) 3._____(dates) Approve for length of treatment; maximum 6 months.	**No**: Pass to RPh. Deny; medical appropriateness
10. Is the claim for moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness
11. Is the patient currently receiving another monoclonal antibody for asthma (e.g., omalizumab, mepolizumab, benralizumab or reslizumab)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #12

Approval Criteria		
12. Has the patient required at least 1 hospitalization or ≥ 2 ED visits in the past 12 months while receiving a maximally-dosed inhaled corticosteroid (Table 1) AND 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, theophylline)?	**Yes:** Go to #13 Document number of hospitalizations or ED visits in past 12 months: _____. This is the baseline value to compare to in renewal criteria.	**No:** Pass to RPh. Deny; medical appropriateness.
13. Has the patient been adherent to current asthma therapy in the past 12 months?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness.

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

Renewal Criteria		
~~2.~~3. Is the patient currently taking an inhaled corticosteroid and 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, theophylline)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.
~~3.~~4. Has the patient reduced their systemic corticosteroid dose by ≥50% compared to baseline?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh. Deny; medical appropriateness.

P&T/DUR Review: *7/19 (DM)*
Implementation: *TBD*
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Monoclonal Antibodies for Severe Asthma

Goal(s):

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

Length of Authorization:

- Up to 12 months

Requires PA:

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

Covered Alternatives:

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

Table 1. Maximum Adult Doses for Inhaled Corticosteroids.

High Dose Corticosteroids:	**Maximum Dose**
Qvar (beclomethasone)	320 mcg BID
Pulmicort Flexhaler (budesonide)	720 mcg BID
Alvesco (ciclesonide)	320 mcg BID
Aerospan (flunisolide)	320 mcg BID
Arnuity Ellipta (fluticasone furoate)	200 mcg daily
Flovent HFA (fluticasone propionate)	880 mcg BID
Flovent Diskus (fluticasone propionate)	1000 mcg BID
Asmanex Twisthaler (mometasone)	440 mcg BID
Asmanex HFA (mometasone)	400 mcg BID
High Dose Corticosteroid / Long-acting Beta-agonists	**Maximum Dose**
Symbicort (budesonide/formoterol)	320/9 mcg BID
Advair Diskus (fluticasone/salmeterol)	500/50 mcg BID
Advair HFA (fluticasone/salmeterol)	460/42 mcg BID
Breo Ellipta (fluticasone/vilanterol)	200/25 mcg daily
Dulera (mometasone/formoterol)	400/10 mcg BID

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is the request for omalizumab, mepolizumab, reslizumab, or benralizumab?	**Yes:** Go to #5	**No:** Go to #4
4. Is the request for a newly approved monoclonal antibody for severe asthma and does the indication match the FDA-approved indication?	**Yes:** Go to #9	**No:** Go to #5
5. Is the claim for reslizumab in a patient under 18 years of age?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #6
6. Is the claim for mepolizumab or benralizumab in a patient under 12 years of age?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #7
7. Is the claim for omalizuamb in a patient under 6 years of age?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #8
8. Is the claim for mepolizumab in an adult patient diagnosed with eosinophilic granulomatosis with polyangiitis (EGPA) for at least 6 months that is refractory to at least 4 weeks of oral corticosteroid therapy (equivalent to oral prednisone or prednisolone 7.5 to 50 mg per day)?	**Yes:** Approve 300 mg (3 x 100mg syringes) every 4 weeks x 1 year	**No:** Go to #9
9. Does the patient have a concurrent prescription for EpiPen® or equivalent so they are prepared to manage delayed anaphylaxis if it occurs after monoclonal antibody therapy?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
10. Is the diagnosis an OHP-funded diagnosis? Note: chronic urticaria is not an OHP-funded condition	**Yes:** Go to #11	**No:** Pass to RPh. Deny; not funded by the OHP.
11. Is the prescriber a pulmonologist or an allergist who specializes in management of severe asthma?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness.
12. Has the patient required at least 1 hospitalization or ≥ 2 ED visits in the past 12 months while receiving a maximally-dosed inhaled corticosteroid (Table 1) AND 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, theophylline)?	**Yes:** Go to #13 Document number of hospitalizations or ED visits in past 12 months: _____. This is the baseline value to compare to in renewal criteria.	**No:** Pass to RPh. Deny; medical appropriateness.
13. Has the patient been adherent to current asthma therapy in the past 12 months?	**Yes:** Go to #14	**No:** Pass to RPh. Deny; medical appropriateness.
14. Is the patient currently receiving another monoclonal antibody for asthma (e.g., omalizumab, mepolizumab, benralizumab or reslizumab)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #15
15. If the claim is for omalizumab, can the prescriber provide documentation of allergic IgE-mediated asthma diagnosis, confirmed by a positive skin test or in vitro reactivity to perennial allergen?	**Yes:** Approve once every 2-4 weeks for up to 12 months. Document test and result:_____	**No:** Go to #16

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

Renewal Criteria		
1. Is the request to renew mepolizumab for EGPA?	**Yes:** Go to #2	**No:** Go to #3
2. Have the patient's symptoms improved with mepolizumab therapy?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is the patient currently taking an inhaled corticosteroid and 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, theophylline)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.
4. Has the number of ED visits or hospitalizations in the last 12 months been reduced from baseline, or has the patient reduced their systemic corticosteroid dose by ≥50% compared to baseline?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh. Deny; medical appropriateness.

Drug Use Research & Management Program
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Drug Class Review with New Drug Evaluation: Narcolepsy Agents

Date of Review: July 2019
Generic Name: solriamfetol

End Date of Literature Search: 05/16/2019
Brand Name (Manufacturer): Sunosi™ (Jazz Pharmaceuticals, Inc.)
Dossier Received: Yes

Research Questions:

1. What is the evidence for efficacy of solriamfetol for the treatment of excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea (OSA) and how does it compare to current therapy?
2. Is solriamfetol safe for the treatment of excessive daytime sleepiness?
3. Are there subpopulations of adults (i.e. age, gender, ethnicity, disease severity, or comorbid conditions) for whom solriamfetol is more effective or associated with more harms?
4. What is the evidence for efficacy or safety of sodium oxybate for the treatment of narcolepsy, and are there subpopulations for which sodium oxybate is more effective or associated with more harms?

Conclusions:

Solriamfetol

- In patients with narcolepsy, solriamfetol was associated with improvement in sleep latency (measured by the maintenance of wakefulness test [MWT]) compared to placebo after 12 weeks of treatment (low quality evidence; mean difference [MD] with 150 mg of 7.65 minutes; 95% CI 3.99 to 11.31).[1]
- There is moderate quality evidence that solriamfetol improves scores on the Epworth sleepiness scale (ESS) over 12 weeks in patients with moderate to severe narcolepsy (with average difference in scores of 2.2 to 4.7 points).[1] The clinical significance of these differences is unclear.
- In patients with OSA, there is low quality evidence that treatment with solriamfetol improves ESS scores an average of 1.9 to 4.5 points and MWT by 4.5 to 10.7 compared to placebo after 12 weeks of treatment.[2]
- There is no data comparing solriamfetol to other treatments for narcolepsy or OSA, and it is unclear if the observed changes in ESS score or MWT correlate to actual changes in functional status, quality of life, occupation, or social life.
- There is insufficient evidence to assess long-term safety or efficacy of solriamfetol. Solriamfetol labeling has warnings for psychiatric adverse events (including anorexia, anxiety/nervousness, insomnia, irritability) which were observed in clinical trials.[3] Patients with an acute or untreated psychiatric conditions were excluded from clinical trials and the effectiveness or safety in these populations is unclear. FDA labeling recommends only using solriamfetol with caution in these patient populations.
- Solriamfetol use was associated with increases in blood pressure and heart rate. During the clinical trial program, 6 patients treated with solriamfetol experienced cardiovascular events compared to no patients in the placebo group.[4] However, differences in major cardiovascular events are small and studies

were not powered to determine differences in long-term outcomes. Because patients with any acute, uncontrolled medical condition were excluded from trials, the risk of long-term cardiovascular events in patients with comorbid conditions is unclear. Food and Drug Administration (FDA) labeling recommends against use of solriamfetol in patients with uncontrolled blood pressure and suggests routine monitoring during treatment.[3] Given that solriamfetol has predominate renal metabolism and excretion it is not recommended for treatment in patients with end stage renal disease (ESRD).[3]

Sodium Oxybate

- There is low strength evidence that use of sodium oxybate 9 gm daily in patients with narcolepsy and cataplexy improves number of cataplexy attacks (median difference of 12 attacks per week compared to placebo), symptoms of narcolepsy (mean difference from placebo of 4-5 points on the ESS) and sleep latency (MWT of 10 to 11 minutes). There is insufficient evidence for benefit at lower doses.[5]
- In pediatric patients 7 to 16 years of age experiencing more than 14 cataplexy attacks over 2 weeks, the number of patient-reported cataplexy attacks was unchanged in patients with continued use of sodium oxybate (median attacks per week 0.3) compared to patients randomized to placebo withdrawal (median increase of 12.7 attacks per week; low strength evidence).[5]
- FDA labeling for sodium oxybate contains warnings for neuropsychiatric reactions, central nervous system and respiratory depression, and risk of abuse and misuse. Due to risk of abuse and significant safety concerns, it is only available through a Risk Evaluation and Mitigation Strategy (REMS) program.

Recommendations:

- Add solriamfetol to the Other Stimulants preferred drug list (PDL) class as FDA-approved medication prescribed for "Sleep-Wake" disturbances.
- Designate solriamfetol as voluntary non-preferred and sodium oxybate as non-preferred based upon the current review of efficacy and safety data.
- Recommend implementation of a safety edit for solriamfetol (**Appendix 3**). Safety edits restrict use to FDA-approved ages and doses and include assessment of cardiovascular disease and renal impairment.

Background:

Obstructive sleep apnea (OSA) is defined by repeated upper airway obstruction events with complete or partial apnea during sleep.[6] Diagnosis of OSA is typically confirmed by polysomnography with at least 15 confirmed events per hour or more than 5 events per hour associated with symptoms such as daytime sleepiness, loud snoring, or gasping during sleep.[6] OSA can be categorized based on the number of events per hour ranging from mild disease (5-15 events/hour) to severe disease (≥30 events/hour).[6] OSA occurs most commonly in patients who are overweight, male, or elderly and often occurs in conjunction with comorbid conditions such as hypertension, heart failure, atrial fibrillation, coronary artery disease, stroke, and metabolic syndrome. Untreated OSA is a known risk factor for major cardiovascular events, traffic accidents, and increased mortality.[6] First-line non-pharmacological treatments of OSA include weight reduction in patients who are overweight and continuous positive airway pressure (CPAP) in patients with moderate to severe OSA.[6] In patients who are unresponsive to or unable to tolerate CPAP, other oral appliances may be used as second line therapy.[6] Stimulant medications may be used in conjunction with first-line non-pharmacological treatment to improve excessive daytime sleepiness, but should not be used as monotherapy as they do not correct the underlying disease process. Medications currently FDA-indicated for OSA and narcolepsy include modafinil, armodafinil, and solriamfetol.

Narcolepsy is a clinical syndrome of daytime sleepiness with cataplexy, hypnagogic hallucinations, and sleep paralysis. It is one of the most common causes of disabling daytime sleepiness after obstructive sleep apnea and is characterized by at least 3 months of excessive daytime sleepiness (EDS).[7] Narcolepsy can have a substantial impact on a patient's occupation, education, ability to drive, sexual life, and personality.[4-6] Therefore, the general well-being of patients with narcolepsy is significantly influenced with consequent bad health perception, challenging psychosocial impact, and negative life effects.[4-6] The International

Classification of Sleep Disorders (ICSD-3) classifies the disease in two subtypes: narcolepsy type 1 (NT1) and type 2 (NT2).[7] Type 1 is characterized by cataplexy, a sudden loss of muscle function triggered by strong emotions, or a proven undetectable amount of hypocretin-1 in the cerebrospinal fluid.[7] In type 2, there is no cataplexy and no proven hypocretin-1 deficiency.[7] Diagnosis is typically based on polysomnography (PSG) and a multiple sleep latency test (MSLT) of less than or equal to 8 minutes and at least 2 sleep onset REM periods.[7] Estimated prevalence of narcolepsy ranges from between 25 and 50 per 100,000 individuals in the general population and incidence of narcolepsy with cataplexy varies from 0.02% to 0.067% in North America and worldwide.[8-10] Many other conditions produce such sleepiness and can mimic or coexist with a hypersomnia of central origin such as narcolepsy and it is estimated that narcolepsy is over diagnosed by as much as 50%.[8-10] These differential diagnoses may include sleep disordered breathing syndromes, periodic limb movements, insufficient sleep, psychiatric disorders, medications, and circadian rhythm disorders. [8-10] All of the aforementioned need to be considered in the differential diagnosis as possibly causing or contributing to the excessive sleepiness in a patient with a hypersomnia of central origin. [8-10] According to the American Academy of Sleep Medicine, first-line pharmacological options for patients with narcolepsy include modafinil or methylphenidate.[7] Second-line pharmacological options include sodium oxybate, armodafinil, or combination treatment with 2 agents.[7] Unlike other treatments, sodium oxybate is a central nervous system depressant indicated for narcolepsy. In patients with cataplexy, sodium oxybate may be a reasonable treatment choice though it has high potential for abuse and may be associated with serious side effects including psychosis, confusion, and sedation.[7] Other drugs used off-label for cataplexy include tricyclic antidepressants and fluoxetine, but the quality of published clinical evidence varies.[8]

Common outcomes used in clinical trials to evaluate symptom improvement include the maintenance of wakefulness test (MWT), Epworth sleepiness scale (ESS), and scales to assess overall patient improvement and disease severity. MWT, which requires patients to fight against sleepiness in a soporific situation, is designed to evaluate the severity of sleepiness in patients suffering from Obstructive Sleep Apnea (OSA) or hypersomnia of central origin (Narcolepsy Type I and II).[11,12] The MWT evaluates sleep latency (measured objectively in minutes via electroencephalogram) and is often used in conjunction with the MSLT to comprehensively evaluate the patient's ability to fall asleep (MSLT) and their ability to stay awake (MWT) in a quiet, non-stimulating setting. Because it is conducted in a laboratory setting, however, the MWT may not accurately reflect a patients' typical sleep performance.[11,12] For both the MSLT and the MWT, there have been no large, multicenter, prospectively collected data to establish normative values, and data from smaller, more limited studies have been utilized to extrapolating thresholds for diagnostic and clinical significance.[11,12] In patients with narcolepsy, mean sleep latency on the 40-min MWT of less than 8.0 minutes has been considered abnormal, and values of 8 to 40 minutes are of uncertain significance.[11,12] When used to evaluate the response to a stimulant or CPAP treatment, there are no established thresholds for a change in mean sleep latency. Potential differences in MSLT and MWT significance between the patients with pathologic conditions and non-pathologic conditions are not clear and suggest that states of sleepiness and wakefulness are manifested differently within patient populations.[11,12] Despite apparent limitations, the MWT still provides the strongest support of an individual's ability to stay awake, and the AASM (American Academy of Sleep Medicine) has called this standard "an appropriate expectation for individuals requiring the highest level of safety".[11,12]

The ESS measures the propensity of a patient to fall asleep in daily situations. Patients rate 8 theoretical scenarios on a 0 to 3 scale (total scores range from 0 to 24) with higher scores indicating greater daytime sleepiness. An ESS score of greater than or equal to 10 indicates excessive sleepiness which requires further assessment.[13] Because the ESS is designed to assess sleepiness rather than chronic fatigue (a condition which can exist independently from sleepiness), it may not adequately assess fatigue due to chronic conditions such as multiple sclerosis (MS).[13,14] Studies suggest that changes of 20-25% on the ESS (corresponding to approximate differences of 4-6 points for patients with severe symptoms) may represent clinically meaningful differences in patients with narcolepsy, but consistent thresholds to evaluate clinically meaningful differences have not been established.[14] Overall patient improvement and disease severity are often evaluated with the clinical global impression of severity scale (CGI-S) and clinical global impression of change scale (CGI-C). CGI-C is a clinician rated scale with scores range from 1 (very much improved) to 7 (very much worse).[12] Similarly, CGI-S evaluates clinician-rated disease severity on a 1 to 7 scale with greater scores indicating greater disease severity.

Previous reviews evaluating evidence for modafinil and armodafinil have not identified clinically significant comparative differences in efficacy or harms between modafinil and armodafinil. There is insufficient evidence on health outcomes (i.e., wakefulness, executive functioning, adverse reactions) as well as off-label dosage consideration to delineate any changes to preferred or non-preferred status. Currently modafinil and armodafinil are designated as voluntary non-preferred on the Oregon Health Plan (OHA) preferred drug list (PDL) and are subject to safety edits. Evidence for modafinil and armodafinil was last reviewed in 2015, and off-label use of these agents is evaluated in a separate report from the Drug Effectiveness Review Project. Sodium oxybate and solriamfetol have not yet been reviewed by the Pharmacy and Therapeutics (P&T) committee. Sodium oxybate was FDA-approved in 2002, is currently designated as a physical rather than mental health drug, and has very limited utilization in fee-for-service. Solriamfetol was recently FDA-approved in 2019 and will be designated as a mental health carve-out drug.

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 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.

Drug Review: Sodium Oxybate
Systematic Reviews:
At the time of this review, no high quality systematic reviews evaluating comparative efficacy or safety of sodium oxybate were identified.

Guidelines:
No high quality guidelines including sodium oxybate were identified.

Randomized Controlled Trials:
A total of 48 citations were manually reviewed from the initial literature search. After further review, 44 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining 4 trials are summarized in the table below.

Sodium oxybate was FDA approved in 2002 and is indicated for treatment of cataplexy or excessive daytime sleepiness due to narcolepsy in patients at least 7 years of age.[15] Efficacy of sodium oxybate has been evaluated in several major randomized, placebo-controlled trials (**Table 1**). Most studies were of low quality due to unclear randomization, allocation concealment, and risk for attrition bias.[16-20] One study had risk for reporting bias as prespecified secondary endpoints were unclear, data for reported outcomes were not available for all groups (e.g., functional outcome questionnaires), or authors reported significant conflicts of interest with the manufacturer funding the study.[16-18] Another had high risk of performance bias due to unclear blinding methods.[20] Applicability was limited by

significant exclusion criteria and run-in periods to titrate off current therapy and assess baseline characteristics.[16-20] Compared to placebo in patients with narcolepsy and cataplexy, sodium oxybate 9 grams per day demonstrated a reduction in the median number of cataplexy attacks per week (-16 vs. -4 attacks with placebo),[20] improvement in ESS score (5 vs. 0.5 points),[16-18] and improvement of approximately 10 minutes in the median MWT at 4 to 8 weeks.[16-18]

One study assessed treatment in pediatric patients 7 to 16 years of age with narcolepsy with cataplexy.[5] The study assessed outcomes over a 2 week randomized withdrawal period for patients on established therapy with sodium oxybate.[5] The trial was discontinued early based on a pre-planned interim analysis which demonstrated benefit, and only 63 patients entered the randomization phase. After 2 weeks, the number of patient-reported cataplexy attacks was unchanged in patients continued on treatment (median attacks per week 0.3) and increased in patients randomized to placebo (median attacks per week 12.7).[5] Secondary outcomes of CGI-C for severity of cataplexy attacks and ESS also demonstrated consistent benefits versus placebo.[5] Data is limited by significant exclusion criteria which limit applicability, unclear randomization and allocation concealment methods, early trial discontinued, and significant differences in efficacy which may lead to unblinding of treatment groups.

Table 1. Summary of Pivotal Studies Completed for Sodium Oxybate.

Study Design	Comparison	Population	Primary Outcome	Results
Xyrem International Study Group[16-18] DB, PC, MC, RCT N=401 screened N=353 enrolled N=285 randomized N=228 analyzed Randomization preceded by a 14 day lead-in period; 21 day withdrawal from other anti-cataplectic therapy, 5-18 day washout period, and 14-21 day baseline period.	1. Sodium oxybate 4.5 gm per day 2. Sodium oxybate 6 gm per day 3. Sodium oxybate 9 gm per day 4. Placebo Dose was titrated by 1.5 gm weekly Duration: 8 weeks	Patients with narcolepsy with cataplexy with at least 8 cataplexy attacks per week during the baseline period were 42 centers in the United States, Canada, and Europe	Excessive daytime sleepiness as evaluated by ESS and MWT from baseline to 8 weeks	Change in median ESS from baseline to 8 weeks 1. -1.0; difference vs. placebo of 0.5; p=0.093 2. -2.0; difference vs. placebo of 1.5; p<0.001 3. -5.0; difference vs. placebo of 4.5; p<0.001 4. -0.5 Change in median MWT from baseline to 8 weeks 1. 1.75 minutes; difference vs. placebo p=0.110 2. 1.00 minutes; difference vs. placebo p=0.520 3. 10.13 minutes; difference vs. placebo p<0.001 4. 0 minutes
The US Xyrem Multicenter Study Group[20] DB, PC, MC, RCT N=136 Randomization preceded by a 28 day withdrawal period for other anti-cataplectic therapy, 5-28 day washout period, and 14-21 day baseline period.	1. Sodium oxybate 3 gm daily 2. Sodium oxybate 6 gm daily 3. Sodium oxybate 9 gm daily 4. Placebo Duration: 4 weeks	Adults with narcolepsy and at least 3 cataplexy attacks per week (median 21 attacks)	Change from baseline in the weekly cataplexy attacks	Median change in cataplexy attacks per week from baseline to 4 weeks 1. -7.0; difference vs. placebo 3.3; p-value NR 2. -9.9; difference vs. placebo 5.6; p-value NR 3. -16.1; difference vs. placebo 11.8; p<0.0008 4. -4.3

Black, et al.[19] DB, double-dummy, PC, MC, RCT N=278 enrolled N=221 randomized Randomization preceded by a 7-14 day lead-in period and 14 days to evaluate baseline characteristics.	1. Switch to sodium oxybate 2. Continue current modafinil therapy 3. Add sodium oxybate to current modafinil therapy 4. Switch to placebo Duration: 8 weeks	Adults with narcolepsy on current treatment with modafinil (200-600 mg daily) 44 sites in the US, Canada, the Czech Republic, France, Germany, the United Kingdom, Switzerland, and the Netherlands.	20-minute MWT after 8 weeks	Change in mean MWT (minutes) from baseline to 8 weeks 1. 0.58 (SD 5.68); difference vs. placebo 3.3; p<0.001 2. -0.53 (SD 4.36); difference vs. placebo 2.2; p=0.006 3. 2.68 (SD 5.07); difference vs. placebo 5.4; p<0.001 4. -2.72 (SD 4.54) Mean ESS Score at 8 weeks 1. 12; difference vs. placebo of 4; p<0.001 2. 15; difference vs. placebo of 1; p=0.767 3. 11; difference vs. placebo of 5; p<0.001 4. 16
Plazzi, et al.[5] N=106 enrolled N=99 entered dose stabilization phase N=63 randomized (trial discontinued early due to pre-planned interim analysis) DB, PC, MC, withdrawal, RCT Randomization preceded by a 3-10 week titration and 2 week dose stabilization phase day lead-in period and 14 days to evaluate baseline characteristics.	1. Continue sodium oxybate 2. Placebo withdrawal Duration: 2 week randomized withdrawal phase then open-label treatment for 12 months	Chldren 7-16 years of age with narcolepsy with cataplexy with at least 14 attacks over 2 weeks at baseline 30 sites in USA, Finland, France, Italy, and the Netherlands	Change in patient-reported weekly number of cataplexy attacks	Median change in number of cataplexy attacks per week from baseline to 2 weeks 1. 0.3 (IQR -1.0, 2.5) 2. 12.7 (IQR 3.4, 19.8) P<0.001

Abbreviations: DB = double blind; ESS = Epworth Sleepiness Scale; FOSQ = Functional Outcomes of Sleep Questionnaire; IQR = interquartile range; MC = multicenter; MWT = maintenance of wakefulness test; NR = not reported; PC = placebo-controlled; RCT = randomized controlled trial; SD = standard deviation; US = United States

Similar to other medications FDA-indicated for narcolepsy, FDA labeling for sodium oxybate contains warnings for neuropsychiatric reactions including hallucinations, paranoia, psychosis, aggression, agitation, depression, and suicidality.[15] Parasomnias, including sleepwalking, have also been reported in approximately 6% of patients treated with sodium oxybate during clinical trials.[15] Sodium oxybate has box warnings for central nervous system and respiratory depression and risk of abuse and misuse.[15] Illicit use has been associated with adverse reactions such as seizures, respiratory depression, loss of consciousness, coma, and death. Operation of machinery or vehicles is not recommended for at least 6 hours after taking sodium oxybate, and it is contraindicated in combination with sedative hypnotics or alcohol.[15] Similarly, sodium oxybate should be used cautiously in patients with sleep-related breathing disorders or compromised respiratory function as central apneas and clinically relevant desaturation events have been reported with treatment. Due to risk of abuse and significant safety concerns, it is only available through a Risk Evaluation and Mitigation Strategy (REMS) program.[15] Other significant safety concerns include caution in patients with heart failure, renal impairment or hypertension as sodium oxybate contains a significant amount of sodium (550 mg of sodium per 3

gram dose).[15] Sodium oxybate is contraindicated in patients with succinic semialdehyde dehydrogenase deficiency, a rare disorder of inborn error of metabolism variably characterized by mental retardation, hypotonia, and ataxia.[15]

In 3 controlled adult clinical trials in patients with narcolepsy, the most common adverse reactions (incidence ≥5% and twice the rate seen with placebo) in sodium oxybate-treated patients were nausea, vomiting, dizziness, somnolence, enuresis, and tremor.[15] Approximately 10% of patients discontinued treatment due to adverse events compared with 3% of patients receiving placebo.[15] Similar adverse events were reported in a trial of pediatric patients 7 years of age and older with narcolepsy, and common adverse reactions included enuresis (18%), nausea (17%), vomiting (16%), headache (16%), weight decreased (12%), decreased appetite (8%), and dizziness (6%).[15]

New Drug Evaluation: Solriamfetol

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

Clinical Efficacy:

FDA approval for solriamfetol was based on one phase II trial and 4 phase III clinical trials in patients with narcolepsy or OSA. One ongoing, long-term phase 3 clinical trial in patients with OSA or narcolepsy remains unpublished and is only summarized briefly here. Primary endpoints included in phase III studies were the change in the MWT and change in the patient-reported ESS. For all studies, exclusion criteria were broad and significantly limit applicability in patients with comorbid diagnoses, acute conditions, or mild disease. Specific inclusion and exclusion criteria are listed in **Table 3**.

In patients with narcolepsy, over 60% of patients had marked or severe illness with an average baseline ESS score of 17 (score range 0 to 24 with scores ≥ 10 indicating excessive sleepiness) and sleep latency of approximately 7 minutes.[1] In the phase 3 study, the average change from baseline to 12 weeks in MWT was statistically significant for solriamfetol 150 mg compared to placebo (MD of 7.65 minutes; 95% CI 3.99 to 11.31; p<0.0001) but was not statistically significant for 75 mg daily (MD 2.26 minutes; 95% CI -1.04 to 6.28; p=0.1595).[1] Change in ESS at 12 weeks was statistically improved with both solriamfetol doses compared to placebo with mean differences of 2.2 to 3.8 points.[1] Evidence was limited by differential attrition rates between groups (ranging from 7 to 17% for FDA-approved doses).[1] Results from this phase III study were supported by a phase II RCT of 93 narcolepsy patients in the United States randomized to 150-300 mg/day or placebo.[3] At 12 weeks, patients treated with solriamfetol had a larger change from baseline in MWT compared to placebo (12.8 vs. 2.1 minutes; p<0.0001).[3] The proportion of patients with improvement in CGI-C (defined as a score of 1-3) was greater with solriamfetol compared to placebo (86% vs. 38%; p<0.0001).[3]

In patients with OSA, almost 70% of patients were adherent to primary OSA therapy at baseline.[2,21] Included patients had moderate to severe OSA with an average ESS score at baseline of 15.[2,21] Treatment with solriamfetol improved ESS an average of 1.9 to 4.5 points compared to placebo from baseline to 12 weeks for various FDA-approved doses.[2] Change in MWT was also consistently statistically significant with solriamfetol at 12 weeks with improvements ranging from 4.5 to 10.7 minutes compared to placebo.[2] A dose response was observed for all outcomes. Evidence was limited by high risk for attrition and reporting bias and unclear risk for selection bias. Though adequate randomization and allocation concealment methods were used, there were differences in baseline characteristics between groups. An enriched, randomized, withdrawal study of 75 to 300 mg solriamfetol provided supporting evidence in OSA.[21] Evidence from this trial has limited applicability as a significant proportion of patients did not meet initial eligibility criteria or discontinued treatment during the titration and dose stabilization run-in period. However, patients who were randomized to continue solriamfetol had a significant decline in mean sleep latency (11.2 minutes; 95% CI 7.8 to 14.6; p<0.0001) and ESS scores (-4.6; 95% CI -6.4 to -2.8; p<0.0001) compared to discontinuation of solriamfetol over 2 weeks.[21]

Patients who completed phase 3 trials for solriamfetol were eligible to be enrolled in an open label 6 month extension study.[4] After more than 6 months, patients were randomized to continue solriamfetol or switch to open-label placebo over 2 weeks.[4] Because outcomes for this study (ESS, PGI-C and CGI-C) were patient and provider reported, there is significant risk for performance bias with these results. There were 640 patients enrolled in the trial with a mean baseline ESS of 16 and 282 patients were included in the randomized withdrawal period after at least 6 months.[4] The average change in ESS score during the withdrawal period was 5.3 (standard error 0.4) points for placebo and 1.6 (SE 0.4) points with continued solriamfetol use (MD of -3.7; 95% CI -4.8 to -2.7).[4] Results were similar in patients with OSA or narcolepsy. Approximately 28% of patients continuing solriamfetol reported worsening on the CGIC or PGIC compared to 64% of patients randomized to placebo.[4]

There is no data comparing solriamfetol to other pharmacologic treatments for narcolepsy or OSA and it is unclear if the observed changes in ESS score or MWT correlate to actual changes in functional status, quality of life, occupation, or social life.

Clinical Safety:
Solriamfetol has been studied in 930 patients with narcolepsy or OSA, 396 of which received an FDA-recommended dose of solriamfetol and 255 patients who received treatment for more than 6 months.[3,4] The majority of data included participants prescribed solriamfetol for 12 weeks though safety data also included one trial evaluating efficacy and safety up to 6 months. Common adverse events were consistent with other stimulant medications and included headache, nausea, decreased appetite, anxiety, and insomnia.[3] Adverse reactions appeared to be dose-related and typically resolved with dose reduction or treatment discontinuation. Discontinuations due to adverse events occurred in 3% of patients receiving FDA-approved doses compared to less than 1% of patients who received placebo.[3] Adverse events leading to discontinuation included anxiety (n=2), palpitations (n=2), and restlessness (n=2). Though studied at higher doses, the FDA-recommended maximum dose for solriamfetol was set at 150 mg daily because doses above this threshold do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.[4]

Because psychiatric adverse events (including anorexia, anxiety/nervousness, insomnia, irritability) were observed in clinical trials, solriamfetol should be used cautiously in patients with pre-existing psychosis or bipolar disorder with adequate monitoring to assess for possible emergence or exacerbation of psychiatric symptoms.[3] Patients with a history of psychiatric conditions were excluded from clinical trials and the effectiveness or safety in these populations is unclear.

Slight increases in blood pressure and heart rate were observed in clinical trials with solriamfetol compared to placebo. At 12 weeks, there was an increase in the maximal mean systolic blood pressure (2.4-4.9 mmHg), diastolic blood pressure (1.8-4.2 mmHg), and heart rate (2.9-4.9 beats per minute) from baseline in patients prescribed 37.5 to 150 mg of solriamfetol.[3] Comparatively in the placebo group, the maximal mean change in systolic blood pressure, diastolic blood pressure, and heart rate at 12 weeks was 1.7-3.5 mmHg, 1.4-1.8 mmHg, and 1.7-2.3 beats per minute, respectively.[3] Though the average change in systolic and diastolic blood pressure was small in clinical trials, chronic elevations in blood pressure have been shown to increase the risk of major adverse cardiovascular events.[3] Patients with narcolepsy and OSA often also have multiple other cardiovascular risk factors and average body mass index indicates that the majority of enrolled patients were either overweight or obese. In these clinical trials, patients with any acute medical condition were excluded and the number of patients with comorbid diagnoses such as hypertension, diabetes, and hyperlipidemia were not reported. During the clinical trial program, 6 patients treated with solriamfetol experienced cardiovascular events compared to no patients in the placebo group.[4] However, differences in major cardiovascular events are small and studies were not powered to determine differences in long-term outcomes. It is unclear what impact solriamfetol may have in populations with significant comorbid diagnoses or increased risk for cardiovascular adverse events. FDA labeling recommends against use of solriamfetol in patients with uncontrolled blood pressure and suggests routine monitoring during treatment.[3] Caution should be taken when prescribing solriamfetol in patients at higher risk of

cardiovascular events, in patients with known cardiovascular or cerebrovascular disease, or in patients with moderate to severe renal impairment as they may be at higher risk for adverse events.[3]

Solriamfetol is contraindicated in patients also receiving treatment with a monoamine oxidase inhibitor due to increased risk of hypertensive reactions.[3] Solriamfetol also has a risk of abuse and has been designated as a schedule IV substance by the Drug Enforcement Agency.

FDA-required post-marketing studies include evaluation of maternal and fetal outcomes for women exposed to solriamfetol while pregnant or breast feeding. In animal studies, fetal toxicities, maternal toxicities and adverse effects on growth and development when administered at 4 to 7 times the maximum recommended human dose.[3]

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Symptom improvement (sleep, fatigue, wakefulness)
2) Quality of life
3) Functional impairment
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Change in the maintenance of wakefulness test (MWT)
2) Change in the Epworth Sleepiness Scale (ESS)

Table 2. Pharmacology and Pharmacokinetic Properties.[3]

Parameter	
Mechanism of Action	Solriamfetol is a dopamine and norepinephrine reuptake inhibitor. It's mechanism of action to improve wakefulness is unclear, but is thought to be related to dopamine and norepinephrine reuptake in the brainstem arousal systems.
Oral Bioavailability	95%
Distribution and Protein Binding	Volume of distribution: 199 liters 13-19% protein bound
Elimination	95% eliminated unchanged in urine. Dose adjustment is recommended in patients with moderate to severe renal impairment.
Half-Life	7.1 hours
Metabolism	NA

Abbreviations: NA = not applicable

Table 3. Comparative Evidence Table.

Ref./ Study Design	Drug Regimen /Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Thorpy, et al.[1] TONES 2 Phase 3 RCT, DB, MC, PC	1. Solriamfetol 300 mg once daily 2. Solriamfetol 150 mg once daily 3. Solriamfetol 75 mg once daily 4. Placebo Titration to target dose was achieved by day 4 Duration: 12 weeks	Demographics: - Mean age (SD) 36.2±13.2 - Female 65.3% - White 80.1% - Mean BMI 28.3 kg/m2 - Cataplexy 50.8% - MWT sleep latency (SD): 7.5±5.7 minutes - ESS score (SD) 17.2±3.2 - CGI-S moderate: 26% - CGI-S marked or severe: 61% Key Inclusion Criteria: - Narcolepsy type 1 or 2 - 18-75 years old - Sleep latency <25 minutes - ESS score ≥ 10 - Patient-reported total sleep time ≥ 6 hours - BMI of 18-45 kg/m^2 Key Exclusion Criteria: - Clinically relevant untreated medical, psychiatric or behavioral disorder associated with excessive sleepiness - History or presence of any acutely unstable medical disorder, psychiatric disorder, or surgical history that could affect patient safety - Current use of medications which could affect excessive sleepiness or cataplexy	ITT: 239 randomized; 231 included in mITT population; NR for each group mITT: (patients who received ≥1 dose and had ≥1 post-baseline assessment) 1. 59 2. 55 3. 59 4. 58 Attrition: 1. 16 (27.1%) 2. 4 (7.3%) 3. 10 (16.9%) 4. 6 (10.3%)	Primary Endpoints (change from baseline to week 12): MWT(minutes) 1. 12.3 (SE 1.4) 2. 9.8 (SE 1.3) 3. 4.7 (SE 1.3) 4. 2.1 (SE 1.3) 1 vs. 4: 10.14 (95% CI 6.39 to 13.90); p<0.0001 2 vs. 4: 7.65 (95% CI 3.99 to 11.31); p<0.0001 3 vs. 4: 2.26 95% CI -1.04 to 6.28); p=0.1595 ESS score 1. -6.4 (SE 0.7) 2. -5.4 (SE 0.7) 3. -3.8 (SE 0.7) 4. -1.6 (SE 0.7) 1 vs. 4: -4.7 (95% CI -6.6 to -2.9); p<0.0001 2 vs. 4: -3.8 (95% CI -5.6 to -2.0); p<0.0001) 3 vs. 4: -2.2 (95% CI -4.0 to -0.3); p=0.0211 Secondary Endpoint: Proportion of Patients with Improvement in Patient Global Impression of Change 1. 84.7% 2. 78.2% 3. 67.8% 4. 39.7% 1 vs. 4: MD 45%; p<0.0001 2 vs. 4: MD 38.5%; p<0.0001 3 vs. 4: MD 28.1%; NS	NA NA 45%/3 38%/3 NS	Study withdrawal due to AE 1. 5 (8.5%) 2. 3 (5.1%) 3. 1 (1.7%) 4. 1 (1.7%) Serious AE 1. 0 (0%) 2. 1 (1.7%) 3. 0 (0%) 4. 0 (0%)	NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: UNCLEAR; use of interactive voice or web response system for randomization and allocation concealment. Patients were stratified based on presence of cataplexy. Average baseline MWT of 6.1 min for placebo and ≥7.5 minutes for solriamfetol. Other baseline characteristics appear balanced. Performance Bias: LOW. Patients and providers blinded with use of identical opaque capsules. Detection Bias: LOW. Patients and providers blinded with use of identical opaque capsules. Attrition Bias: HIGH. Significant attrition in treatment groups ranging from 7-27%. Imputation was performed based on an average of other assessments for MWT and ESS if there were less than 2 or 3 missing values respectively. Sensitivity analyses performed using different imputation approaches found no substantial differences in treatment effect. Reporting Bias: LOW. Study protocol not available but outcomes reported as specified. Other Bias: UNCLEAR; Funding provided by Jazz Pharmaceuticals who was involved in protocol design and assisted with data collection, analysis and interpretation of data. **Applicability**: Patient: Significant exclusion criteria limit applicability in patients with comorbid conditions or those with acute illness. Included patients had primarily moderate to severe illness. Intervention: FDA approved dose of solriamfetol is 75-150mg daily. Comparator: Placebo appropriate to determine efficacy. Comparison to current treatments such as modafinil or armodafinil may help establish place in therapy. Outcomes: Frequent follow-up at 1, 4, 8, and 12 weeks may not reflect current practice. Significant placebo response for patient reported outcomes. Setting: 50 sites in the United States and Canada. 9 sites in Finland, France, Germany, and Italy.

2. Schweitzer, et al.[2] TONES 3 Phase 3 RCT, DB, MC, PC, PG	1. Solriamfetol 300 mg once 2. Solriamfetol 150 mg once 3. Solriamfetol 75 mg once 4. Solriamfetol 37.5 mg once 5. Placebo Titration to target dose was achieved by day 4 Duration: 12 weeks	Demographics: - Mean age: 54 years - Male: 56-64% - White: 73-79% - BMI: 33 kg/m^2 - mean MWT 12-13 min - mean ESS score: 15 - CGI-S moderate: 37-50% - CGI-S marked: 24-37% - CGI-S severe: 11-15% - Adherent to OSA therapy: 68-73% - H/o surgery: - Placebo: 18% - Solriamfetol: 13% Key Inclusion Criteria: - OSA diagnosis - 18-75 years old - ESS score ≥ 10 - Sleep latency <30 min - Usual patient-reported total sleep time ≥ 6 hours - Current use of primary OSA therapy including mandibular advancement device, PAP, or surgical intervention - In patients without current OSA therapy or with a history of surgery, at least one month of prior primary OSA therapy was required Key Exclusion Criteria: - Bedtime later than 1 am - Job requiring shiftwork - Current drug use which could affect excessive sleepiness or cataplexy - Current or past moderate to severe substance use disorder, nicotine dependence affecting sleep, or other clinically	ITT: 1. 119 2. 118 3. 61 4. 59 5. 119 mITT (patients who received ≥1 dose and had ≥1 post-baseline assessment): 1. 115 2. 116 3. 58 4. 56 5. 114 Attrition: 1. 25 (21.0%) 2. 12 (10.2%) 3. 7 (11.5%) 4. 10 (17.0%) 5. 18 (15.1%)	Primary Endpoints (change from baseline to week 12): MWT (minutes) 1. 13.0 2. 11.0 3. 9.1 4. 4.7 5. 0.2 1 vs. 5: 12.8 (95% CI 10 to 15.6); p<0.0001 2 vs. 5: 10.7 (95% CI 8.1 to 13.4); p<0.0001 3 vs. 5: 8.9 (95% CI 5.6 to 12.1); p<0.0001 4 vs. 5: 4.5 (95% CI 1.2 to 7.9); p<0.0086 ESS score 1. -7.9 2. -7.7 3. -5.0 4. -5.1 5. -3.3 1 vs. 5: -4.7 (95% CI -5.9 to -3.4); p<0.0001 2 vs. 5: -4.5 (95% CI -5.7 to -3.2); p<0.0001 3 vs. 5: -1.7 (95% CI -3.2 to -0.2); p=0.0233 4 vs. 5: -1.9 (95% CI -3.4 to -0.3); p=0.0161 Secondary Endpoint: Proportion of Patients with Improvement in PGI-C 1. 88.7% 2. 89.7% 3. 72.4% 4. 55.4% 5. 49.1% 1 vs. 5: 39.6 (95% CI 28.7 to 50.4); p<0.0001 2 vs. 5: 40.5 (95% CI 29.8 to 51.3); p<0.0001 3 vs. 5: 23.3 (95% CI 8.6 to 38.0); p=0.0035	NA NA 40%/3 40%/3 23%/5	Study withdrawal due to AE 1. 16 (13.6%) 2. 5 (4.3%) 3. 2 (3.2%) 4. 3 (5.2%) 5. 4 (3.4%) Serious AE 1. 0 (0%) 2. 1 (0.8%) 3. 0 (0%) 4. 2 (3.3%) 5. 2 (1.7%)	NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: UNCLEAR; use of interactive voice or web response system for randomization and allocation concealment. Patients were stratified based on adherence to primary OSA therapy. Differences in baseline characteristics between groups including CGI-S, race, sex, history of surgical intervention, and adherence to primary OSA therapy. Performance Bias: LOW. Patients and providers blinded with use of identical capsules. Detection Bias: LOW. Patients and providers blinded with use of identical capsules. Attrition Bias: HIGH. Significant attrition in treatment groups ranging from 10-21%. It is unclear how missing data was handled. Reporting Bias: HIGH. All secondary endpoints not reported including functional outcomes, productivity, and health related quality of life. Other Bias: UNCLEAR; Funding provided by Jazz Pharmaceuticals who was involved in protocol design. Data collected by investigators and analyses were conducted by a contract research organization under supervision of the study sponsor. Potential conflicts of interest were not reported for study authors. **Applicability**: Patient: The majority of patients enrolled had moderate to severe illness. Patients with comorbid conditions which may contribute to sleep problems were excluded. Similarly, patients with moderate to severe substance use disorder were excluded. Solriamfetol is a schedule IV substance. Intervention: FDA approved dose of solriamfetol is 75-150mg daily. Follow-up with patients was done at 1, 4, 8, and 12 weeks which may not reflect current practice. Comparator: Placebo appropriate to determine efficacy. Comparison to current treatments such as modafinil or armodafinil may help establish place in therapy. Outcomes: Frequent follow-up at 1, 4, 8, and 12 weeks may not reflect current practice. Significant placebo response for patient reported outcomes.

		relevant behavioral, medical, or psychiatric disorder associated with excessive sleepiness		4 vs. 5: 6.2 (95% CI -9.7 to 22.2); p=0.4447	NS			Setting: 59 research sites in the United States, Canada, France, Germany, and the Netherlands between May 19, 2015, and December 23, 2016
3. Strollo, et al.[21] TONES 4 Phase 3 RCT, DB, MC, PC, enriched, withdrawal study	1. Continuation of solriamfetol 75-300 mg 2. Placebo withdrawal from solriamfetol treatment Phase 1: dose titration to 75mg, 150mg, or 300mg every 3 days to maximize efficacy and tolerability Phase 2: stable dose phase Phase 3: DB randomized withdrawal phase Duration: 6 weeks total (2 weeks during randomized phase)	Demographics (DB period): - Mean age: 56 years - Male: 58-66% - White: 72-81% - CGI-S moderate or markedly ill: 65.5% - Primary OSA therapy: 76-79% - ESS Score: 15-16 - MWT: 12-13 minutes - BMI: 33 kg/m2 - FOSQ-10 Score: 14 Key Inclusion Criteria: - OSA diagnosis - Age 18 to 75 years - Current or prior primary OSA therapy including CPAP, oral appliance or surgical intervention - BMI < 45 kg/m^2 - ESS score ≥ 10 - Sleep latency < 30 min - Usual patient-reported total sleep time ≥ 6 hours - Patients with much or very much improvement on the PGI-C scale during the stable dose phase Key Exclusion Criteria: - Diagnoses other than OSA associated with excessive sleepiness - Nighttime or variable shift work - Excessive caffeine use 1 week prior to the study (definition of excessive use not provided) - Nicotine dependence which affects sleep	ITT: Screened: 402 Phase 1: 174 Phase 2: 157 Phase 3: 124 1. 62 2. 62 mITT (excluded 1 patient who withdrew consent and 1 patient who failed to meet randomization criteria): 1. 60 2. 62 Attrition: 1. 2 (3.2%) 2. 0 (0%)	Primary Endpoint: Change during phase 3 in MWT mean sleep latency (SE) 1. -1.0 (1.4) minutes 2. -12.1 (1.3) minutes MD 11.2 (95% CI 7.8 to 14.6); p<0.0001 Change during phase 3 in ESS score 1. 4.5 (0.7) 2. -0.1 (0.7) MD -4.6 (95% CI -6.4 to -2.8); p<0.0001 Secondary Endpoint: Proportion of patients during phase 3 with decline in PGI-C score 1. 20% 2. 50% Difference -30% (95% CI -46 to -14); p<0.001 Proportion of patients during phase 3 with decline in CGI-C score 1. 21.7% 2. 59% Difference -37.3% (95% CI -53.5 to -12.2); p<0.0001 Change from phase 1 to end of phase 2 or 3 in FOSQ-10 score 1. 16.4 (SD 2.9) 2. 17.4 (SD 3.0) MD 1.2 (95% CI 0.2 to 2.1); p<0.05	NA NA 30%/4 37%/3 NA	Study withdrawal due to AE 6 (3.4%) during titration phase Serious AE 0 (0%)	NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: UNCLEAR. Randomization stratified by adherence to primary OSA therapy. Methods of randomization and allocation concealment were not specified. Baseline characteristics differed between groups for randomized phase. More white and female patients were enrolled in continued treatment. Performance Bias: UNCLEAR. Methods of blinding were not specified. Use of patient and provider reported symptom and functional outcomes may increase risk of bias Detection Bias: UNCLEAR. Methods of blinding were not specified. MWT scored by a central reader. Attrition Bias: LOW. Attrition low and similar between groups. Prior to randomization, 29% of enrolled patients discontinued treatment (n=29) or did not meet eligibility criteria for phase 3 (n=21; PCG-C scale of much or very much improved). Reporting Bias: LOW. Protocol unavailable but all outcomes reported as specified. Other Bias: HIGH. Primary author involved in data analysis and writing manuscript had financial conflicts of interest in the form of consultancy fees and honoraria from the manufacturer. All others including employees of the manufacturer were involved in study design, collection, analysis and interpretation of data and writing the article. **Applicability**: Patient: 4 week run-in titration/stabilization period. Only patients who tolerated treatment and were much or very much improved at 4 weeks were eligible for randomization. Significant exclusion criteria limits applicability. Intervention: During the stable dose phase, 14.6% of patients received 75 mg, 31.8% received 150mg and 53.5% of patients received 300 mg. Comparator: Placebo appropriate to determine efficacy.

		- Surgical history that could affect participant - Any acutely unstable medical, behavioral or psychiatric condition - Current drug use which could affect excessive sleepiness or cataplexy						Outcomes: No long-term outcome data available and there was no difference in functional outcome assessments. Setting: Sites in Finland, France, Germany, Sweden and the United States from May 2015 to November 2016

Abbreviations : AE = adverse effect; BMI = body mass index; CGI-C = clinician global impression of change; CGI-S = clinician global impression of severity; CI = confidence interval; DB = double-blinded; DEA = drug enforcement agency; ESS = Epworth sleepiness scale; FOSQ-10 = functional outcomes of sleep questionnaire; H/o = history of; ITT = intention to treat; MD = mean difference; mITT = modified intention to treat; MC = multi-center; MWT = maintenance of wakefulness test; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = non-significant; PAP = positive airway pressure; PC = placebo-controlled; PG = parallel-group; PP = per protocol; RCT = randomized controlled trial; SD = standard deviation; SE = standard error; US = United States; YO = years old

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Appendix 1: Prescribing Information Highlights

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

SUNOSI (solriamfetol) tablets, for oral use, CIV
Initial U.S. Approval: 2019

INDICATIONS AND USAGE

SUNOSI is a dopamine and norepinephrine reuptake inhibitor (DNRI) indicated to improve wakefulness in adult patients with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea (OSA). (1)

Limitations of Use
SUNOSI is not indicated to treat the underlying airway obstruction in OSA. Ensure that the underlying airway obstruction is treated (e.g., with continuous positive airway pressure (CPAP)) for at least one month prior to initiating SUNOSI for excessive daytime sleepiness. Modalities to treat the underlying airway obstruction should be continued during treatment with SUNOSI. SUNOSI is not a substitute for these modalities. (1)

DOSAGE AND ADMINISTRATION

- Administer once daily upon awakening. Avoid administration within 9 hours of planned bedtime because of the potential to interfere with sleep. (2.2)
- Starting dose for patients with narcolepsy: 75 mg once daily. (2.3)
- Starting dose for patients with OSA: 37.5 mg once daily. (2.4)
- Dose may be increased at intervals of at least 3 days. (2.3, 2.4)
- Maximum dose is 150 mg once daily. (2.3, 2.4)
- Renal impairment (2.5, 8.6, 12.3):
  - Moderate impairment: Starting dose is 37.5 mg once daily.
    - May increase to 75 mg once daily after at least 7 days.
  - Severe impairment: Starting dose and maximum dose is 37.5 mg once daily.
  - End stage renal disease (ESRD): Not recommended.

DOSAGE FORMS AND STRENGTHS

Tablets: 75 mg (functionally scored) and 150 mg. (3)

CONTRAINDICATIONS

Concurrent treatment with a monoamine oxidase inhibitor (MAOI) or use of an MAOI within the preceding 14 days. (4)

WARNINGS AND PRECAUTIONS

- *Blood Pressure and Heart Rate Increases*: Measure heart rate and blood pressure prior to initiating and periodically throughout treatment. Control hypertension before and during therapy. Avoid use in patients with unstable cardiovascular disease, serious heart arrhythmias, or other serious heart problems. (5.1)
- *Psychiatric Symptoms*: Use caution in treating patients with a history of psychosis or bipolar disorders. Consider dose reduction or discontinuation of SUNOSI if psychiatric symptoms develop. (5.2)

ADVERSE REACTIONS

Most common adverse reactions (≥ 5% and greater than placebo): headache, nausea, decreased appetite, insomnia, and anxiety. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Jazz Pharmaceuticals, Inc. at 1-800-520-5568 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

Drugs that Increase Blood Pressure and/or Heart Rate and Dopaminergic Drugs: Use caution when co-administering with SUNOSI. (7.2, 7.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 06/2019

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) 1946 to June Week 3 2019

1	sodium oxybate.mp. or exp Sodium Oxybate/	1792
2	exp Narcolepsy/	3653
3	1 and 2	224
4	limit 3 to (english language and humans)	206
5	limit 4 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or equivalence trial or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	48

Appendix 3: Proposed Safety Edit

Solriamfetol Safety Edit

Goal(s):

- Promote safe use of solriamfetol in patients with narcolepsy and obstructive sleep apnea.

Length of Authorization:

6 to 12 months

Requires PA:

- Solriamfetol

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

Approval Criteria		
3. Is the diagnosis funded by OHP? Non-funded diagnoses: • Shift work disorder (ICD10 G4720-4729; G4750-4769; G478) • Unspecified hypersomnia (ICD10 G4710)	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Is the request for continuation of therapy at the maintenance dose previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #5
5. Is the patient 18 years of age or older?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness; Recommend preferred alternative methylphenidate. Providers for patients 7 to 17 years of age may also submit a request for sodium oxybate as it is FDA- approved for narcolepsy in this age group.
6. Is the drug prescribed by or in consultation with an appropriate specialist for the condition (e.g., sleep specialist, neurologist, or pulmonologist)?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the request for less than or equal to 150 mg daily?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Is the request for concurrent use with a monoamine oxidase inhibitor?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #9

Approval Criteria		
9. Is there baseline documentation of fatigue severity using a validated measure (e.g., Epworth score, Brief Fatigue Inventory, or other validated measure)?	**Yes:** Go to #10 Document baseline scale and score	**No:** Pass to RPh. Deny; medical appropriateness
10. Is there documentation of a recent cardiovascular risk assessment (including blood pressure) with physician attestation that benefits of therapy outweigh risks?	**Yes:** Go to #11 Document recent blood pressure within the last 3 months and physician attestation of cardiovascular risk assessment	**No:** Pass to RPh. Deny; medical appropriateness Use of solriamfetol is not recommended in patients with uncontrolled hypertension or serious heart problems.
11. Does the patient have a diagnosis of end stage renal disease?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #14
12. Is the request for treatment of narcolepsy?	**Yes:** Approve for up to 6 months	**No:** Go to #15
13. Is the request for treatment of obstructive sleep apnea and has the patient been stable and adherent to primary OSA treatment (such as CPAP or other primary therapy) for at least one month?	**Yes:** Approve for up to 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is the request for treatment of obstructive sleep apnea?	**Yes:** Go to #2	**No:** Go to #3
2. Is the patient adherent to primary OSA treatment (e.g., CPAP) based on chart notes?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is there documentation of a recent blood pressure evaluation (within the last 3 months)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
4. Is there documentation of clinical benefit and tolerability from baseline? The same clinical measure used to diagnose excessive daytime sleepiness or fatigue is recommended to document clinical benefit.	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 7/19 (SS)
Implementation: TBD

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

OHSU Drug Effectiveness Review Project Summary Report – Off-label Use of Modafinil (Provigil™) and Armodafinil (Nuvigil™)

Date of Review: May 2019

Date of Last Review: September 2015
End Date of Literature Search: 2/8/2019

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

Research Questions:
1. What is the effectiveness of modafinil or armodafinil when prescribed above FDA-approved dosages for approved and off-label indications (e.g., narcolepsy, obstructive sleep apnea [OSA], cancer- or multiple sclerosis [MS]-related fatigue, or major depressive disorder [MDD]?
2. What are the harms of modafinil or armodafinil when prescribed above FDA-approved dosages?

Conclusions:
- There is insufficient comparative evidence for efficacy or harms for either modafinil and/or armodafinil in doses exceeding current FDA labeling for OSA, cancer- or MS-related fatigue and MDD (**Table 1**).[1]

Modafinil
- Two trials of fair methodologic quality with modafinil dosing beyond current FDA labeling (200 to 400mg) for narcolepsy demonstrated improvement in morning and midday sleep latency with statistical and clinical significance as compared to placebo (**Table 1**). However, caution is warranted in interpreting these findings given their low grade of evidence (**Table 1**).[1]
- There was no difference between the two modafinil doses at any time point or for any outcome within either investigation aforementioned (**Table 1**).[1]
- As with other stimulants, discontinuation of modafinil resulted in a return of both objective and subjective sleepiness. However, there was not a pattern of amphetamine-like withdrawal symptoms. During the discontinuation phase of this study, no patients reported withdrawal emergent adverse experiences.[1]

Armodafinil
- One trial with poor methodologic quality compared armodafinil 150 and 250 mg/day to placebo in individuals with narcolepsy; however, evidence was insufficient to draw conclusions (**Table 1**).[1]
- Armodafinil has not been studied in children for any medical indication, and use is not recommended in children.[2-5]

Author: Kara Shirley, PharmD, BCPS, BCPP, BCACP and Sarah Servid, PharmD.

Safety

- DRESS (drug reaction with eosinophilia and systemic symptoms), also known as multi-organ hypersensitivity, has been reported with modafinil and armodafinil. Post-marketing reports have included 2 fatalities associated with DRESS and hypersensitivity following recent initiation of armodafinil. Armodafinil should be discontinued at the first sign of rash, skin or mouth sores, blistering or ulceration.[2-5]
- FDA labeling was revised to emphasize the risk of psychiatric symptoms, including suicidal ideation, with use of armodafinil. Symptoms may result in hospitalization and have occurred with any dose (50 to 450 mg daily).[2-5]

Recommendations:

- No changes to the preferred drug list (PDL) are recommended for modafinil or armodafinil based on the current review of efficacy and safety data.
- Update safety edits to include assessment of first-line therapy in patients with OSA and alternative options for treatment in children.

Summary of Prior Reviews and Current Policy

- Previous reviews have not identified clinically significant comparative differences in efficacy or harms between modafinil and/or armodafinil. There is insufficient evidence on health outcomes (i.e., wakefulness, executive functioning, adverse reactions) as well as off-label dosage consideration to delineate any changes to preferred or non-preferred status. Currently both medications are designated as voluntary non-preferred on the Oregon Health Plan (OHA) preferred drug list (PDL) (**Appendix 1**).
- In an analysis of Oregon Medicaid claims data in 2015, funded off-label diagnoses were associated with 26.5% of patients prescribed armodafinil or modafinil. This data prompted implementation of the current policy that limits modafinil and armodafinil use to FDA approved or evidence-based dosages and indications.
- Current safety edits for modafinil and armodafinil require a 90-day trial with evidence of efficacy for continued use (**Appendix 4**) and 74% of utilization is for modafinil with 26% utilization for armodafinil within the FFS population.

Methods:

The March 2019 drug class report on the Off-label Use of Modafinil (Provigil™) and Armodafinil (Nuvigil™) by the Drug Effectiveness Review Project (DERP) at the Center for Evidence Based Policy at Oregon Health & Science University (OHSU) was synthesized to inform recommendations for this drug class and written summary. 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:

Both armodafinil and modafinil are often prescribed above FDA maximum dose and for off-label conditions including fatigue associated with cancer, MS and other neurological conditions, depression, and other mood disorders. An evaluation of modafinil prescriptions in the U.S. (between 2002 and 2009) found that 89% of prescriptions were for off-label conditions.[1] In Oregon Medicaid, prior authorization (PA) requests for modafinil and armodafinil currently account for approximately 5% of all PAs evaluated, and a significant proportion of providers request therapy above the FDA-recommended maximum dose. An analysis of efficacy and/or harms related to modafinil and armodafinil therapy with high, off-label dosage regimens was completed by DERP in March of 2019 to evaluate appropriateness of current dosage limits.[1] A search ending in February 2019 identified 13 studies which compared on-label and off-label dosages (5 RCTs and 8

uncontrolled interventional trials): 7 in individuals with narcolepsy, 1 in individuals with obstructive sleep apnea (OSA), 2 in individuals with multiple sclerosis (MS), and 3 in individuals with depression (MDD partial responders).[1]

For inclusion within the DERP report, trials were required to compare at least 2 different dosages of modafinil or armodafinil. If medication was compared solely to a placebo or the comparative dosages did not exceed the current FDA maximum, the investigation was subsequently excluded from the DERP summary.[1] Two RCTs were graded as having fair methodological quality and the remaining 11 studies graded are of poor methodological quality.[1] Quality grades are reflective of industry involvement in all of the studies included (e.g., funding, study conduct).[1] Additionally, studies were further downgraded because of poor or unclear reporting of methods, no control group, small numbers of participants, brevity of study duration and follow-up, lack of intention-to-treat analysis, and lack of statistical adjustment for differences in baseline characteristics.[1] Few published studies followed up beyond a short treatment period (e.g., 2 to 3 weeks); therefore, it is challenging to conclude whether adverse events were acute or chronic or whether efficacy is sustained over long-term treatment.[1] Studies with results comparing efficacy of different dosages are detailed in **Table 1**.

Studies included within the DERP report evaluated excessive daytime sleepiness as a primary treatment outcome measure.[1] Common tests used to evaluate excessive daytime sleepiness included the clinician-rated multiple sleep latency test (MSLT), the maintenance of wakefulness test (MWT), and the patient-rated Epworth Sleepiness Score (ESS).[1] Additional clinical outcomes evaluation scales are detailed in **Table 1** and **Appendix 3 Table 2**.[1]

Table 1. Modafinil & Armodafinil: Studies with results reported by dose[1]

Comparison	Study Design & Population	Outcome	Clinical Findings	Evidence Strength
Narcolepsy				
U.S. Modafinil in Narcolepsy Multicenter Study Group (1998) Modafinil: 200 mg Modafinil: 400 mg Placebo	RCT; 9 weeks + up 40 weeks of open-label extension N = 283 • Adults 18–68 years • MSLT score < 8 minutes • Age (mean years): 42 • Gender (female): 54.4%	• Wakefulness (ESS, MSLT, MWT) • Clinical condition (CGI-C) • Adverse events	Outcomes evaluated at 9 weeks; mean ± SD **MWT** • 200 mg: 8.1 ± 6.1 minutes (compared to placebo p < 0.001) • 400 mg: 8.9 ± 6.2 minutes (compared to placebo p < 0.001) • Placebo: 5.1 ± 4 7 minutes (results only reported in figure; NS from baseline) **ESS** • 200 mg: 14.4 ± 5.7 minutes (compared to placebo p < 0.001) • 400 mg: 13.0 ± 5.7 minutes (compared to placebo p < 0.001) • Placebo: 17.0 ± 5.0 minutes (compared to baseline p <0.001) **MSLT** • 200 mg: 4.7 ± 4.4 minutes (compared to placebo p < 0.001) • 400 mg: 5.2 ± 4.5 minutes (compared to placebo p < 0.001) • Placebo: 3.3 + 3.2 minutes (results only reported in figure; NS from baseline) **CGI-C (percentages only available in publication figure)** • 200mg: weeks 3,6,9 and endpoint p < 0.005 • 400mg: weeks 3,6,9 and endpoint p < 0.005	**Fair**

<table>
<tr><td></td><td></td><td></td><td>• Placebo: NS (clinical or statistical) in any group at any time; weeks 3,6,9 and endpoint</td><td></td></tr>
<tr><td>U.S. Modafinil in Narcolepsy Multicenter Study Group (2000)
Modafinil: 200 mg
Modafinil: 400 mg
Placebo</td><td>RCT; 9 weeks + up 40 weeks of open-label extension
N = 271
• Adults 17–67 years
• MSLT score ≤ 8 minutes
• ≥ 2 sleep onset REM periods
• No prior modafinil use
• Age (mean years): 42
• Gender (female): 54.4%</td><td>• Wakefulness (ESS, MSLT, MWT)
• Clinical condition (CGI-C)</td><td>Outcomes evaluated at 9 weeks; mean ± SD
MWT
• 200 mg: 8.2 ± 5.9 minutes (placebo and baseline p <0.001)
• 400 mg: 7.8 ± 5.3 minutes (placebo and baseline p <0.001)
• Placebo: 5.5 ± 4.5 minutes (results only reported in figure; NS from baseline)

ESS
• 200 mg: 13.0 ± 5.1 minutes (placebo and baseline p < 0.001)
• 400 mg: 12.3 ± 5.1 minutes (placebo and baseline p < 0.001)
• Placebo: 15.8 ± 4.8 minutes (change from baseline p < 0.001)

MSLT
• 200 mg: 4.9 ± 4.3 minutes (placebo p < 0.001; change form baseline p < 0.03)
• 400 mg: 5.1 ± 4.0 minutes (placebo and baseline p < 0.001)
• Placebo: 3.5 ± 3.4 minutes (change from baseline p < 0.001)

Patients with CGI-C improvement from baseline:
<table><tr><td></td><td>No change</td><td>Minimal</td><td>Much</td><td>Very Much</td></tr><tr><td>400 mg</td><td>29%</td><td>27%</td><td>27%</td><td>9%</td></tr><tr><td>200 mg</td><td>33%</td><td>23%</td><td>26%</td><td>6%</td></tr><tr><td>Placebo</td><td>47%</td><td>24%</td><td>14%</td><td>0%</td></tr></table></td><td>Fair</td></tr>
<tr><td colspan="5">Obstructive Sleep Apnea</td></tr>
<tr><td>Modafinil for Obstructive Sleep Apnea (OSA)
Black et al. (2005)
Modafinil: 200 mg
Modafinil: 400 mg
Placebo</td><td>RCT
12 weeks + 12-month open-label extension
N = 309

• Aged 18–70 years,
• ESS score ≥ 10,
• using nCPAP therapy
• Age (mean years):48.4
• Gender (female):22.4%</td><td>• Wakefulness (MWT, ESS)
• Clinical condition (CGI-S, CGI-C)
• Sleep-related functional status (FOSQ)
• Nighttime sleep and nCPAP use (PSG)
• Adverse events</td><td>MWT
• 1.6 minutes and 1.5 minutes (P > 0.15) between dosages
ESS
• both dosages had a drop of 4.5 points compared to placebo (p-value NS)
CGI-C
• 200mg: 61%
• 400mg: 68%
• Placebo 37%
• 200mg vs. 400 mg: 7% (p-value not reported)
• 200 mg vs. placebo: 24% (P<0.001).
FOSQ (change from baseline for patients given modafinil)
• 6 months SD ± 2.43 ± 2.67 (p < 0.0001)
• 12 months SD ± 2.08 ± 2.71 (p < 0.0001)
Adverse Events (Top 3 for each dosage regimen & placebo)
• Headache 13 to 26% (p=0.02 combined modafinil vs placebo respectively)
• Nausea 2% to 10% (p=0.01 for combined modafinil vs placebo respectively)
• Infection 22% to 10% (p=0.1 combined modafinil vs placebo respectively)</td><td>Poor</td></tr>
</table>

Abbreviations: CGI-C: Clinical Global Impression of Change scale; CGI-S: Clinical Global Impression of Severity scale; ESS: Epstein Sleepiness Scale; FOSQ: Functional Outcomes of Sleep Questionnaire; MSLT: Multiple Sleep Latency Test; MWT: Maintenance of Wakefulness Test; nCPAP = nasal continuous positive airway pressure; NS = nonsignificant; RCT: randomized controlled trial; SD: standard deviation; PSG: polysomnography;

Armodafinil

Narcolepsy

One double-blind RCT of poor quality evaluated armodafinil 150 and 250 mg/day compared to a placebo in individuals with narcolepsy for 12 weeks.[1] Individuals diagnosed with narcolepsy were required to have a rating of "moderately ill" (i.e., ≥4 on the Clinical Global Impression of Severity scale [CGI-S]) and a mean sleep latency of less than or equal to 6 minutes on the MSLT.[1] Due to inadequate statistical power, statistical differences for alleviation of excessive daytime sleepiness, fatigue, or overall clinical condition could not be evaluated between active dosage regimens. Upon comparison of 150mg and 250mg, there was no difference in the proportion of patients who had minimally, much, and very much improvement on the Clinical Global Impression of Change (CGI-C) scale from baseline to 12 weeks (21% vs. 20% for minimal, 33% vs. 35% for much, and 16% vs. 18% for very much improvement for 150 mg and 250 mg, respectively).[1] Comparatively, in patients randomized to placebo, 17% had minimal improvement, 12% were much improved, and 3% were very much improved. Both armodafinil doses were associated with statistically significant improvements in memory, attention, and fatigue as measured by the MWT.[1] The mean change in Maintenance of Wakefulness (MWT) from baseline at final visit for armodafinil was an increase of 1.3, 2.6, and 1.9 minutes from baseline in the 150 mg, 250 mg, and combined groups, respectively, compared with a decrease of 1.9 minutes for placebo ($p < 0.01$ for all three active treatments vs. placebo). Adverse reactions reported more commonly with armodafinil compared to placebo were headache, nausea, and dizziness.[1] Dose-dependent differences in cardiovascular function (e.g., blood pressure) were observed, but differences were small and the clinical significance of these small mean changes is unclear.[1]

Other Indications

At the time of this DERP Summary Report is no published evidence for armodafinil doses greater than or equal to 250 mg/day for OSA, MS-related fatigue, cancer-related fatigue, or depression.[1]

Modafinil

Narcolepsy

Five RCTs (4 parallel group trials and one crossover trial) and one uncontrolled interventional study in narcoleptic individuals evaluated modafinil dosages ranging from 200 to 600 mg/day.[1] Of the 5 RCTs, 3 had poor and 2 had fair methodological quality, and only 2 parallel group RCTs directly compared dose effects.[1] While most studies included in the DERP report were of poor quality, this summary focuses primarily on the fair quality trials. Further detail regarding modafinil narcolepsy studies of poor methodologic quality may be found within the full DERP report.[1]

The U.S. Modafinil in Narcolepsy Multicenter Study Group (1998) was a double-blind, parallel-group, placebo-controlled RCT of modafinil in narcolepsy patients (n=283). Patients were 18 to 68 years of age with a current diagnosis of narcolepsy based on the International Classification of Sleep Disorders.[1] Patients were included if they met the following criteria: 1) recurrent daytime naps or lapses into sleep occurring almost daily for at least 3 months, 2) sudden bilateral loss of postural muscle tone in association with intense emotion (cataplexy), and 3) less than 8 minutes of sleep latency on the MSLT. All participants had 2 or more sleep onset rapid eye movement periods and were free of medical or behavioral health conditions that could account for narcolepsy symptoms. The primary study endpoints were MWT and CGI-C compared to placebo, and secondary outcomes included CGI-S, ESS, and MSLT. Outcomes were measured at 3, 6, and 9 weeks. The percentage of subjects with improved independent clinician assessment of illness on the CGI-C was statistically and clinically significant for the

modafinil 200-mg and 400-mg treatment groups compared with placebo at weeks 3, 6, and 9 and at endpoint (all $p < 0.005$).[1] The percentage of subjects improving on the CGI-C at any timepoint did not differ between the two modafinil groups.[1] The percentage of placebo subjects who improved was also not significant at any assessment at weeks 3, 6 and 9 as compared to baseline.

Modafinil consistently reduced daytime sleepiness on all sleep measures (MWT, MSLT and ESS) and clinician assessment of improvement (CGI-C) compared to placebo, but there was no difference between 200 mg and 400 mg groups (**Table 1**).[1] The MSLT results indicated a magnitude, representativeness, and stability of effect similar to the ESS findings for all treatment groups.[1] Compared to placebo, more subjects in both the modafinil 200 mg and 400 mg treatment groups succeeded in remaining awake for an entire 20-minute MWT test both ($p=0.002$).[1] At baseline, only 3% of those receiving 400 mg modafinil, 4% of those receiving 200 mg modafinil, and 3% of those receiving placebo were able to remain awake for at least three tests. At week 9, the percentage of subjects able to stay awake for at least three MWT tests significantly increased to 20% for the 400 mg modafinil group and 14% for the 200 mg modafinil group in contrast to the placebo group which did not change.[1] Only headache was clinically although not considered statistically significant in a comparison of modafinil to placebo.[1]

A second randomized, placebo-controlled, double-blind, parallel-group trial evaluated two fixed doses of modafinil (200mg and 400mg) compared to placebo.[1] Study assessments were conducted at baseline, at weeks 1, 3, 6, and 9 of the double-blind treatment phase, and at week 2 of the discontinuation phase (week 11 of the study). The primary study endpoints of excessive daytime sleepiness and over clinical condition were assessed using the MWT and CGI-C at baseline and week 9.[1] At baseline, the median time to sleep onset at baseline was approximately 5 minutes. The percent of patients with improved clinician assessment of illness on the CGI-C was greater for modafinil 200 mg (46/80 patients, 58%) and 400 mg treatment groups (51/83 patients, 61%) compared with placebo (32/84 patients, 38%) at week 9 ($p=0.03$ for comparisons to placebo; **Table 1**).[1] The percentage of patients who improved was also greater in both modafinil groups at weeks 3 and 6 as compared to baseline ($p>0.05$). The percent of patients who improved in the modafinil 400 mg treatment group was not significantly greater than the percent of patients who improved in the 200 mg treatment group (**Table 1**).[1] The percent of patients who improved in the placebo treatment group was not statistically or clinically significant at any post baseline CGI-C assessment.[1]

During the 9-week treatment phase, patients in the modafinil 200 mg and 400 mg groups demonstrated a statistically and clinically significant increase in wakefulness as measured by the MWT, ESS, and MSLT compared to placebo but no clinical difference between 200 mg and 400 mg doses (**Table 1**).[1] Although modafinil was an effective therapeutic agent and improved alertness in a profoundly sleepy population, it did not completely resolve the symptoms of EDS **(Table 1)**, and treatment was associated with a significant placebo response (all groups improved in subjective sleepiness [ESS] from baseline; **Table 1**).[1] As with other stimulants, discontinuation of modafinil resulted in a return of both objective and subjective sleepiness. In some cases, rebound symptoms after treatment discontinuation were more severe than symptoms reported at baseline. During the discontinuation phase, there was no observed pattern of amphetamine-like withdrawal symptoms or withdrawal emergent adverse experiences.[1]

Obstructive Sleep Apnea

One open-label extension study of poor methodologic quality compared modafinil at 200 and 400 mg/day for 12 months in 266 participants with OSA (104 additional participants received a placebo).[1] Those who met study inclusion criteria had diagnosed OSA using nasal continuous positive airway pressure (CPAP) and had completed at least 8 weeks of a 12-week double blind treatment period where ESS baseline screening was greater than or equal to 10.[1] Treatment with modafinil at 200 or 400 mg/day increased sleep latency and reduced subjective excessive daytime sleepiness as compared to placebo ($P < 0.0001$) with clinical and statistical significance (CGI-C and FOSQ; **Table 1**).[1] The Functional Outcomes Sleep Questionnaire (FOSQ) assessed the impact of excessive daytime sleepiness (EDS) on functional outcomes relevant to daily activities and quality of life, whereby lower scores indicate greater dysfunction.[1] Modafinil maintained the patients' functional status, as shown by a significant improvement compared with baseline in the mean FOSQ total score (change from baseline ± SD at 6

months was 2.43 ± 2.67 and at 12 months was 2.08 ± 2.71; both p < 0.0001), as well as individual domains of activity level, vigilance, intimacy/sexual relationship, general productivity and social outcome (all p < 0.0001).[1] However, there were no clinically or statistically significant differences in measurements of EDS including mean MWT (1.6 vs. 1.5 minutes; P > 0.15) or ESS (P > 0.15; data not reported) between the two modafinil dosages (**Table 1**).[1] Similarly, there was no difference in overall clinical condition, as measured by the CGI-C, between the 2 modafinil dosages (61% for 200mg and 68% for400mg; **Table 1**).[1] The majority of adverse events were assessed as mild or moderate in severity.[1] Anxiety, nervousness and insomnia occurred in 14 patients and serious adverse events were reported in 13 patients, one of which experienced bradycardia and syncope (**Table 1**).[1]

Fatigue secondary to Multiple Sclerosis (MS)

Two uncontrolled interventional studies of poor methodological quality compared modafinil 200 and 400 mg/day in individuals with MS (n=122; 50 open-label trial and 72 crossover investigation).[1] Many findings from these investigations were published in figure form only and should also be interpreted with caution given their poor methodological quality.[1] Overall, reductions in MS associated sleepiness (ESS) and fatigue (FSS, BFI and VAS-F) were not observed at high doses of 400mg/day compared to baseline. However, in patients prescribed modafinil doses of less than 200mg improvement in sleepiness from baseline was documented.[1] Common adverse events associated with modafinil for MS associated fatigue were headache, anxiety and vertigo. A total of 9 participants discontinued treatment due to adverse events.[1]

Augmentation of Depression "Partial-Responders"

Three studies (one RCT and 2 uncontrolled trials) of poor methodologic quality examined modafinil 50 to 400 mg/day for augmentation of major depression in patients prescribed at least one antidepressant.[1] The majority of participants in these studies received 300 mg/day.[1] Trials did not report results by dosing regimen making valid statistical and/or clinical comparison difficult.[1] In the RCT, there was no statistically significant difference between modafinil and placebo for wakefulness (ESS), fatigue (ESS), overall clinical condition (CGI-C), and depression (HAM-D and MADRS) after 6 weeks of adjunctive modafinil therapy.[1] In a 12-week, uncontrolled open-label extension study evaluating benefit of dose increases in patients on 200 mg modafinil, 69 patients (28%) previously nonresponsive to modafinil at dosages of 200 mg/day found that they had clinically significant therapeutic response in fatigue symptom scores (FSS) and wakefulness (ESS) at dosages of 300 to 400 mg/day. These results were not statistically significant.[1] Common adverse events of modafinil in all depression augmentation studies included headache, anxiety, insomnia, nausea and dizziness (**Table 1**).[1]

Cancer-related Fatigue

No trials were identified for modafinil in dosages greater than or equal to 200 mg/day for cancer-related fatigue.[1]

New FDA Safety Alerts:

Table 2. Description of new FDA Safety Alerts[12]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Armodafinil	Nuvigil®	February 2017	Warnings/Precautions	Serious dermatologic reactions, Drug Reaction with Eosinophilia and System Symptoms (DRESS) and multiorgan hypersensitivity were added to labeling based on postmarketing reports. Post-marketing reports have included 2 fatalities associated with DRESS and hypersensitivity following recent initiation of armodafinil. Armodafinil should be discontinued at the first sign of rash, skin or mouth sores, blistering or ulceration.

				Labeling was also revised to emphasize the risk of psychiatric symptoms, including suicidal ideation, with use of armodafinil. Symptoms may result in hospitalization and have occurred with any dose (50 to 450 mg daily).

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Appendix 1: Current Preferred Drug List

V	armodafinil	TABLET
V	armodafinil (NUVIGIL)	TABLET
V	modafinil	TABLET
V	modafinil (PROVIGIL)	TABLET

Appendix 2: PICOS

Population	Individuals with narcolepsy, obstructive sleep apnea, cancer-related fatigue, multiple sclerosis-related fatigue, or depression
Intervention	Modafinil prescribed above 200 mg/day or armodafinil prescribed above 250 mg/day
Comparator	Any dosage of modafinil or armodafinil or placebo
Outcomes	**Symptom Improvement** Reduction in excessive daytime sleepiness and/or fatigue, psychiatric symptoms **Safety** Misuse and dependence potential Serious Adverse Events Discontinuation from Serious Adverse Events
Timing	Any study duration; literature search through February 8, 2019
Setting	Outpatient

Appendix 3: Summary of Outcomes Rating Scales of Clinical Significance in DERP Report

Questionnaire/Test	*Rater*	*Scale*	*Clinical Significance*
Narcolepsy & OSA			
Maintenance of Wakefulness Test (MWT)[1,6-8]	Clinician	Mean sleep latency on the 40 minutes MWT of < 8 minutes = abnormal and 8 to 40 minutes are of uncertain significance. Direction of change may also serve as a clinical guide in Narcolepsy as well as OSA.	Objectively assesses the ability to remain awake for a defined period of time in a laboratory setting (quiet non-stimulating situation for a given period of time). Concurrent driving simulation testing adds real-world predictive value in occupational assessment. Also used to evaluate individuals who must stay awake for job safety reasons however may not accurately predict performance in real-life circumstances.
Multiple Sleep Latency Test (MSLT)[1, 6-8]	Clinician	Measures an individual's ability to fall asleep in the laboratory setting. The Multiple Sleep Latency Test (MSLT) is a sleep disorder diagnostic tool. It is used to measure the time elapsed from the start of a daytime nap period to the first signs of sleep, called sleep latency. The test is based on the idea that the sleepier people are, the faster they will fall asleep. The test consists of four or five 20-minute nap opportunities set two hours apart, often following an overnight sleep study. During the test, data such as the patient's brain waves, EEG, muscle activity, and eye movements are monitored and recorded. The entire test normally takes about 7 hours during the course of a day.	Mean sleep latency of less than 5 minutes indicates a pathologic level of daytime sleepiness. Normal adults have a mean sleep latency of 10 to 20 minutes. Sleep latency on the screening MSLT < 3min usually indicates marked or severe EDS although distinct sleep latency cutoffs have not been statistically validated due population differences. Can be influenced by sleep up to 7 days before the test the preceding sleep-wake cycle. Interpretation relies on AASM established scoring criteria (last in 2007) inclusive of mean sleep latency of all naps as well as onset to REM sleep.
Epworth Sleepiness Scale (ESS)[11]	Patient	Total scores range from 0 to 24, with higher scores indicating greater sleepiness. Eight scenarios rated from 0 to 3 in terms of how likely the patient feels they would be to fall asleep.	Score is the sum of questions from 8 proposed situations. Higher score indicates increased daytime sleepiness; An ESS score ≥ 10 indicates ES and requires further assessment. An improvement in wakefulness is indicated by a decrease in score.
Clinical Global Impression of Change Scale (CGI-C)[1]	Clinician	CGI-C scores range from 1 (very much improved) through to 7 (very much worse). "Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment."	Each component of the CGI is rated separately; the instrument does not yield a global score.
Functional Outcomes of Sleep Questionnaire (FOSQ)[1]	Patient	Thirty (30) items, 5 factor subscales. Disease specific quality of life questionnaire to determine functional status in adults; measures are designed to assess the impact of disorders of excessive sleepiness on multiple activities of everyday living and the extent to which these abilities are improved by effective treatment.	Activity level, vigilance, intimacy and sexual relationships, general productivity, social outcome, rate the difficulty of performing a given activity on a 4-point scale (no difficulty to extreme difficulty). Lower scores indicate greater dysfunction.
MS-Related Fatigue			
Modified Fatigue Impact Scale (MFIS)[1, 10]	Patient	0 to 84 (lower score indicates less fatigue). The total score for the MFIS is the sum of the scores for the 21 items. Individual subscale scores for physical, cognitive, and psychosocial functioning can also be generated by calculating the sum of specific sets of items.	The MFIS is a modified form of the Fatigue Impact Scale based on items derived from interviews with MS patients concerning how fatigue affects their lives. This instrument provides an assessment of the effects of fatigue in terms of physical, cognitive, and psychosocial functioning.
Visual Analogue Scale for Fatigue (VAS-F)[1, 10]	Patient	0 to 100 (higher score indicates less fatigue) Two subscales: fatigue (items 1–5 and 11–18) and energy (items 6–10). Though individuals do not require training in order to score the scale, developers are quick to point out that high levels of inter-rater reliability are vital if results are to be correctly interpreted.	Consists of 18 items relating to the subjective experience of fatigue. Each item asks respondents to place an "X," representing how they currently feel, along a visual analogue line that extends between two extremes (e.g., from "not at all tired" to "extremely tired"). In contrast to discrete, Likert-type scales, the VAS-F places fewer restrictions on the range of responses available to individuals. However, the benefits of a visual analogue scale may be offset by the frequent reluctance of individuals to use the highest and lowest extremes.

Brief Fatigue Inventory (BFI)[1, 10]	Patient	Patients rated each item using an 11-point scale (0–10), with higher scores indicating greater fatigue severity or impact.	Patient-rated global fatigue (average of all questions) and worst fatigue during the past 24h (Item number 3).
Fatigue Severity Scale of Sleep Disorders (FSS) [1,10]	Patient	Nine (9) statements that rate the severity of fatigue symptoms. Each statement is scored from 1 to 7, based on how accurately it reflects the patient's condition during the past week and the extent to which the patient agrees or disagrees. A low value (e.g., 1) indicates strong disagreement with the statement, whereas a high value (e.g., 7) indicates strong agreement.	Total score of less than 36 suggests that the patient may not be suffering from fatigue. A total score of 36 or more suggests that the patient may need further evaluation.
Clinical Global Impression of Severity Scale (CGI-S)[1]	Clinician	The CGI is rated on a 7-point scale, with the severity of illness scale using a range of responses from 1 (normal) through to 7 (amongst the most severely ill patients).	Each component of the CGI is rated separately; the instrument does not yield a global score.
Depression			
Hamilton Depression Rating Scale (HAM-D)[1]	Clinician	Method for scoring varies by version. For the HDRS17, a score of 0–7 is generally accepted to be within the normal range (or in clinical remission), while a score of 20 or higher (indicating at least moderate severity) is usually required for entry into a clinical trial.	The HDRS (also HAM-D) is the most widely used clinician-administered depression assessment scale. Originally developed for hospital inpatients, thus the emphasis on melancholic and physical symptoms of depression. *A later 21-item version (HDRS21) included 4 items intended to subtype the depression, but which are sometimes, incorrectly, used to rate severity. A limitation of the HDRS is that atypical symptoms of depression (e.g., hypersomnia, hyperphagia) are not assessed.*
Montgomery Asberg Depression Rating Scale (MADRS)[1]	Clinician	Used by clinicians to assess the severity of depression among patients with a diagnosis of depression. It is designed to be sensitive to change resulting from antidepressant therapy. Takes 20-60 minutes to be completed by interview. MADRS is typically interview administered, however it can be self-administered. The MADRS should be used with caution in patients with cognitive impairment as results can be skewed towards higher depression scores, however the MADRS can be used with individuals with aphasia.	Each item has a severity scale from 0 to 6, with higher scores reflecting more severe symptoms. Ratings can be added to form an overall score (from 0 to 60). Scores of 0-6 indicate an absence of symptoms; 7-19 represent mild depression; 20-34 moderate; 35-60 indicate severe depression.
Abbreviations: BFI: Brief Fatigue Inventory; CGI-C: Clinical Global Impression of Change scale; CGI-S: Clinical Global Impression of Severity scale; EEG: Electroencephalogram; ESS: Epstein Sleepiness Scale; FSS: Fatigue Severity Scale; FOSQ: Functional Outcomes of Sleep Questionnaire HAM-D: Hamilton Rating Scale for Depression; MADRS: Montgomery-Asberg Depression Rating Scale; MFIS: Modified Fatigue Impact Scale; MSLT: Multiple Sleep Latency Test; MWT: Maintenance of Wakefulness Test; nCPAP: nasal continuous positive airway pressure; QD: single dose; SD: split dose; VAS-F: Visual Analogue Scale for Fatigue			

Modafinil / Armodafinil (Sleep-Wake Medications)

Goal(s):

- Limit use to diagnoses where there is sufficient evidence of benefit and uses that are funded by OHP. Excessive daytime sleepiness related to shift-work is not funded by OHP.
- Limit use to safe doses.

Length of Authorization:

- Initial approval of 90 days if criteria met; approval of up to 12 months with documented benefit OR doses above those in Table 2.

Requires PA:

- Payment for drug claims for modafinil or armodafinil without previous claims evidence of narcolepsy or obstructive sleep apnea ~~(ICD10 G47411; G47419; G4730; G4731; G4733; G4739)~~

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. Funded Indications.

Indication	Modafinil (Provigil™)	Armodafinil (Nuvigil™)
• Excessive daytime sleepiness in narcolepsy • Residual excessive daytime sleepiness in obstructive sleep apnea patients treated with CPAP.	FDA approved for Adults 18 and older	FDA approved for Adults 18 and older
• Depression augmentation ~~(unipolar or bipolar)~~ (unipolar or bipolar I or II acute or maintenance phase) • Cancer-related fatigue • Multiple sclerosis-related fatigue	Not FDA approved; Low level evidence of inconsistent benefit	Not FDA approved; insufficient evidence
• Drug-related fatigue • Excessive daytime sleepiness or fatigue related to other neurological disorders (e.g. Parkinson's Disease, traumatic brain injury, post-polio syndrome) • ADHD • Cognition enhancement for any condition	Not FDA approved; insufficient evidence	Not FDA approved; insufficient evidence

Table 2. Maximum Recommended Dose (consistent evidence of benefit with lower doses).

Generic Name	Minimum Age	Maximum FDA-Approved Daily Dose
armodafinil	18 years	250 mg
modafinil	18 years	200 mg

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the patient 18 years of age or older?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness. Providers for patients 7 to 17 years of age may also submit a request for sodium oxybate as it is FDA- approved for narcolepsy in this age group.
3. Is this a funded diagnosis? Non-funded diagnoses: • Shift work disorder (ICD10 G4720-4729; G4750-4769; G478) • Unspecified hypersomnia (ICD10 G4710)	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by OHP
4. Is the drug prescribed by or in consultation with an appropriate specialist for the condition (e.g., sleep specialist, neurologist, or pulmonologist)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Will prescriber consider a preferred alternative?	**Yes:** Inform prescriber of preferred alternatives (e.g., preferred methylphenidate)	**No:** Go to #6

Approval Criteria		
6. Is the request for continuation of therapy at maintenance dosage previously approved by the FFS program?	**Yes:** ~~Pass to RPh.~~ Go to Renewal Criteria~~#15~~	**No:** Go to #7
7. Is the prescribed daily dose higher than recommended in Table 2?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #8
~~Is diagnosis narcolepsy or obstructive sleep apnea (ICD10 G47411; G47419; G4730; G4731; G4733; G4739) AND is the drug prescribed by, or in consultation with, a sleep specialist or neurologist?~~	~~**Yes:** Approve for 90 days and inform prescriber further approval will require documented evidence of clinical benefit.~~	~~**No:** Go to #8~~
8. Is the request for treatment of narcolepsy?	**Yes:** Approve for 90 days and inform prescriber further approval will require documented evidence of clinical benefit.	**No:** Go to #9
9. Is the request for treatment of obstructive sleep apnea (OSA) (without narcolepsy) and is the patient compliant with recommended first-line treatments (e.g., CPAP)?	**Yes:** Approve for 90 days and inform prescriber further approval will require documented evidence of clinical benefit.	**No:** Go to #10
10. Is the request for armodafinil?	**Yes:** Pass to RPh. Deny; medical appropriateness. There is insufficient evidence for off-label use.	**No:** Go to #11~~3~~
~~9. Is the diagnosis unipolar or bipolar depression?~~	~~**Yes:** Approve for 90 days and inform prescriber further approval will require documented evidence of clinical benefit.~~	~~**No:** Go to #10~~

Approval Criteria		
~~10. Is the diagnosis MS or cancer-related fatigue?~~ ~~Note: Methylphenidate is recommended first-line for cancer.~~	~~**Yes:** Inform prescriber of first-line options available without PA.~~ ~~May approve for 90 days and inform prescriber further approval will require documented evidence of clinical benefit.~~	~~**No:** Go to #11~~
~~11. Is the diagnosis ADHD?~~	~~**Yes:** Pass to RPh. Deny; medical appropriateness.~~ ~~There is insufficient evidence for benefit for ADHD. See available options at www.orpdl.org/drugs/~~	~~**No:** Go to #12~~
11. Is the primary diagnostic indication for modafinil fatigue secondary to major depression (MDD), MS or cancer-related fatigue? Note: Methylphenidate is recommended first-line for cancer.	**Yes:** Inform prescriber of first-line options available without PA. May approve for 90 days and inform prescriber further approval will require documented evidence of clinical benefit and assessment of adverse effects.	**No:** Go to #12
12. All other diagnoses must be evaluated as to the OHP-funding level and evidence for clinical benefit. • Evidence supporting treatment for excessive daytime sleepiness (EDS) or fatigue as a result of other conditions is currently insufficient and should be denied for "medical appropriateness". • Evidence to support cognition enhancement is insufficient and should be denied for "medical appropriateness". If new evidence is provided by the prescriber, please forward request to Oregon DMAP for consideration and potential modification of current PA criteria.		

Approval Criteria
~~11. Continuation of therapy requires submission of documented evidence of clinical benefit and tolerability (faxed copy or equivalent). The same clinical measure (eg, Epworth score, Brief Fatigue Inventory, or other validated measure) used to diagnose fatigue or depression is recommended to document clinical benefit.~~ ~~• Approve up to 12 months with chart documentation of positive response.~~ ~~Deny for "medical appropriateness" in absence of documented benefit.~~

Renewal Criteria		
1. Is the request for treatment of obstructive sleep apnea?	**Yes:** Go to #2	**No:** Go to #3
2. Is the patient adherent to primary OSA treatment (e.g.,CPAP) based on chart notes?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is there documentation of clinical benefit and tolerability from baseline? The same clinical measure used to diagnose excessive daytime sleepiness (EDS), fatigue secondary to MS and/or cancer, major depressive disorder (MDD) is recommended to document clinical benefit.	**Yes:** Approve for up to 12months	**No:** Pass to RPh. Deny; medical appropriateness

P&T Review: *7/19 ; 03/16; 09/15*
Implementation: *8/16, 1/1/16*

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Drug Class Update with New Drug Evaluation: Bone Metabolism Drugs

Date of Review: July 2019

Generic Name: romosozumab-aqqg

Date of Last Review: March 2018
Dates of Literature Search: January 2018- May 23, 2019
Brand Name (Manufacturer): Evenity™
Dossier Received: yes

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

Purpose for Class Update:
To define place in therapy for a new monoclonal antibody (romosozumab) recently approved by the United States (US) Food and Drug Administration (FDA) for the treatment of osteoporosis in postmenopausal women at high risk for fracture. In addition, new comparative evidence for existing bone metabolism agents (e.g.; bisphosphonates, teriparatide, abaloparatide, zoledronic acid, and denosumab) for management of osteoporosis and Paget disease will be reviewed.

Research Questions:
- Is there new comparative evidence that bone metabolism agents differ in efficacy or effectiveness for osteoporosis?
- Is there any new comparative evidence the bone metabolism agents differ in harms?
- Are there specific subpopulations (gender, fracture risk) for which one agent is better tolerated or more effective than other available agents?
- What is the evidence for efficacy and harms for the new monoclonal antibody, romosozumab, recently approved to treat postmenopausal osteoporosis**?**

Conclusions:
Class Update
- Four new systematic reviews were identified for inclusion in this drug class update.
- An updated systematic review for the US Preventive Services Task Force evaluated recent evidence on screening and treatment to prevent osteoporotic fractures.[1] One large randomized clinical trial (RCT) comparing screening with no screening reported 28% reduction in hip fractures for women with screening (2.6% vs. 3.5%; hazard ratio [HR], 0.72; 95% Confidence Interval [CI] 0.59-0.89; Absolute Risk Reduction [ARR] 0.9%) but no other statistically significant benefits or harms were observed at 5 years' follow-up.[1] Moderate quality evidence showed that for women, bisphosphonates, parathyroid hormone, raloxifene, and denosumab were associated with a lower risk of vertebral fractures (9 trials; relative risks [RRs] from 0.32-0.64].[1] Evidence was limited for men: zoledronic acid reduced the risk of radiographic vertebral fractures (1 RCT, RR 0.33; 95% CI 0.16 to 0.70); no studies demonstrated reductions in clinical or hip fractures.[1] Bisphosphonates were not consistently associated with reported harms, although rare outcomes were not generally observed in the included evidence.[1]

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- A high quality systematic review sponsored by the Agency for Healthcare Research and Quality (AHRQ) summarized the effects of long-term osteoporosis drug treatment and of osteoporosis drug treatment discontinuation and holidays.[2] After 3 to 5 years of treatment, continuation of zoledronate or alendronate versus drug holiday inconsistently reduced incident vertebral fracture outcomes (based on radiographic evidence) only for zoledronate: low strength of evidence (SOE), clinical evidence only for alendronate (moderate SOE), but did not reduce nonvertebral fractures (low SOE).[2]
- A high quality systematic review and meta-analysis compared the efficacy and safety of denosumab with bisphosphonates to treat osteoporosis.[3] There was no significant difference between the risk of fracture (RR 1.13; 95% CI 0.82 to -1.55; P=0.466), adverse events [AEs], (RR 1.00; 95% CI 0.96 to 1.04; P=0.957) and withdrawal due to AEs (RR 0.68; 95% CI 0.34 to 137; P=0.280) between bisphosphonates and denosumab in the meta-analysis.[3] Evidence from this meta-analysis suggests no benefit of denosumab for reducing risk of fracture over bisphosphonates.[3]
- Six studies were included in a high quality systematic review that evaluated the safety and efficacy of romosozumab in the treatment of postmenopausal osteoporosis.[4] The meta-analysis of the trial data showed romosozumab resulted in a significantly lower risk of new vertebral fracture (RR 0.37; 95% CI, 0.18 to 0.77; P=0.008), non-vertebral fracture (RR 0.79; 95% CI, 0.68 to 0.92; P<0.003,) and hip fracture (RR 0.59; 95% CI, 0.42 to 0.83; P=0.002) compared with placebo, alendronate and teriparatide at 24 months (moderate strength of evidence).[4] There was no significant difference in the incidence of adverse events in patients with romosozumab compared to placebo (RR 1.00; 95% CI 0.98 to 1.02; p=0.93) over the 24 month study periods (moderate strength of evidence).[4] Absolute rates were not reported, refer to **Table 2** for a specific study results from the 4 Phase 3 trials with romosozumab.

Romosozumab

- The safety and efficacy of romosozumab were demonstrated in 2 clinical Phase 3 trials involving women with postmenopausal osteoporosis. One additional small Phase 3 trial evaluated the safety and efficacy of romosozumab in men with a history of fracture.
- In the Fracture Study in Postmenopausal Women with Osteoporosis (FRAME) trial, moderate quality evidence shows that romosozumab significantly reduced the incidence of new vertebral fractures compared to placebo during the first 12 months of therapy (0.5% with romosozumab vs. 1.8% with placebo; RR 0.27; 95% CI, 0.16 to 0.47; P<0.001; ARR 1.3%; NNT 77).[5] However, the reduction in non-vertebral fractures at 12 months was not statistically significant (1.6% with romosozumab vs. 2.1% with placebo; P=0.10; 95% CI, 0.53 to 1.05).[5]
- The Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk (ARCH) compared the effects of romosozumab 210 mg SC once monthly with oral alendronate 70 mg once weekly for 12 months, followed by open label alendronate therapy in both treatment groups for up to an additional 2 years.[6] Moderate quality evidence shows after 24 months of therapy, new vertebral fractures occurred in 6.2% of the women who received romosozumab and in 11.9% of alendronate-treated women (RR 0.52; 95% CI, 0.40 to 0.66; P<0.001; ARR 5.7%; NNT 18).[6] In this trial, serious cardiovascular adverse events were observed more often with romosozumab than with alendronate (50 of 2040 patients [2.5%] vs. 38 of 2014 patients [1.9%]) during the first year of therapy.[6]
- The BRIDGE trial was a placebo-controlled study conducted in 245 men with a history of fracture.[7] Moderate quality evidence demonstrates that after 12 months of therapy, the mean percentage change from baseline in the lumbar spine BMD was significantly greater for the romosozumab group than for the placebo group (12.1% vs 1.2% respectively; P < 0.001; 95% CI not reported).[7] Incidence of fracture, the FDA recommended primary endpoint to assess osteoporosis therapy, was not evaluated in this small trial and romosozumab is not currently approved for use in men.
- In the FRAME and ARCH trials, the following adverse reactions that occurred in more than 2% of patients and were associated with romosozumab administration included arthralgia (13.0%), headache (5.8%) and injection site reactions (5.2%).[8]
- The romosozumab drug label has a black box warning regarding the possibility for increased the risk of myocardial infarction, stroke and cardiovascular death associated with romosozumab adminstration.[8] Patients with a history of myocardial infarction or stroke within the past year should not start on romosozumab therapy.[8]

- There is insufficient data for long-term safety and efficacy of romosozumab beyond 12 months of administration. Due to waning efficacy on bone development after 12 months, the FDA has limited duration of romosozumab therapy to 12 months.[8]

Recommendations:

- Maintain romosozumab as a non-preferred agent on the Practitioner-Managed Prescription Drug Plan (PMPDP).
- Update clinical prior authorization (PA) criteria for bone metabolism agents to include romosozumab.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy

Abaloparatide was reviewed by the Pharmacy and Therapeutics Committee at the November 2017 meeting. Abaloparatide was designated as a non-preferred agent on the Practitioner-Managed Prescription Drug Plan (PMPDP) and clinical prior authorization (PA) criteria for bone metabolism agents were updated to include abaloparatide. One systematic review which evaluated the use of bisphosphonates in men was presented to the committee was part of the 2017 class update. Moderate quality evidence shows that bisphosphonates reduce fracture risk for men with osteoporosis.[9] Further studies are needed to evaluate the efficacy of non-bisphosphonate treatment options such as denosumab or teriparatide to reduce vertebral and nonvertebral fracture risk for men.[9] The American College of Endocrinology (AACE/ACE) and American College of Physicians (ACP) recommend alendronate, risedronate, zoledronic acid, or denosumab as first-line treatment options for postmenopausal osteoporosis in their clinical practice guidelines.[10,11] Preferred drugs on the PMPDP for osteoporosis include alendronate, ibandronate and risedronate. Nonpreferred drugs including raloxifene, denosumab, abaloparatide and teriparatide are subject to PA review. Most of the Oregon Health Plan (OHP) Fee-For-Service (FFS) utilization for bone metabolism drugs is due to oral alendronate. The PDL status of the bone metabolism agents is presented in **Appendix 1.**

Background:

Osteoporosis is characterized by low bone mass, deterioration of bone tissue, disruption of bone architecture, compromised bone strength, and increased risk of fracture.[12] According to the World Health Organization (WHO) diagnostic classification, osteoporosis is defined by bone mineral density (BMD) at the hip or lumbar spine that is less than or equal to 2.5 standard deviations (SD) below the mean BMD of a young-adult reference population.[13] Major risk factors for osteoporosis are female gender, elderly age, low BMD, and low intake of calcium and vitamin D.[12] Medications that affect endocrine pathways may also cause secondary osteoporosis.[12] The largest risk group for osteoporosis is post-menopausal women. Although osteoporosis is more prevalent in women, it is estimated that up to one third of new osteoporotic fractures occur in men.[14] Some of the more common secondary causes of osteoporosis in men include glucocorticoid treatment, alcohol abuse, obstructive pulmonary disease, hypogonadism, post-transplantation, and androgen ablation therapy in prostate cancer.[15]

Bone fractures are the clinical consequence of osteoporosis. The most common fractures are those of the vertebrae, hip, and wrist.[12] Risk of fracture can be assessed with the Fracture Risk Assessment (FRAX) Tool, which estimates the 10-year probability of hip fracture and major osteoporotic fracture (spine or forearm) using 9 clinical risk factors including BMD.[16] Hip fractures result in disability related to difficulty with ambulation, inability to perform of activities of daily living, and are associated with increased nursing home and rehabilitation hospital admissions.[17] Approximately 20% of patients who experience hip fractures die within a year of injury.[12] Osteoporosis poses a heavy financial burden on patients, with annual direct medical costs estimated at 17 to 20 billion dollars in the United States.[18] By 2025, annual fractures and associated costs are projected to rise by almost 50%.[19] The most rapid growth in fracture risk is estimated for people 65-74 years of age.[19]

Adult bone is continuously remodeled by osteoclastic bone resorption and osteoblastic bone formation.[20] The drugs used to slow bone loss in osteoporosis are of two categories: anti-resorptive (osteoclast inhibition) and anabolic (osteoblast stimulation). Anti-resorptive agents include bisphosphonates (e.g., alendronate, ibandronate, risedronate, and zoledronic acid), selective estrogen receptor modulators (raloxifene), and a monoclonal antibody (denosumab). The parathyroid hormone analogs, teriparatide and abaloparatide are anabolic agents. The primary goal of osteoporosis management is to reduce fracture risk. Randomized clinical trials demonstrate a reduction of vertebral and hip fractures with bisphosphonates. Alendronate and risedronate also decrease vertebral fractures in men and in patients with glucocorticoid-induced osteoporosis.[21] The main concerns associated with bisphosphonate use are rare side-effects, such as atypical femur fractures and osteonecrosis of the jaw. Raloxifene has been shown to reduce the risk of vertebral, but not non-vertebral, fractures.[17] Although it reduces breast cancer risk, raloxifene increases the incidence of hot flashes and venous thromboembolism. Teriparatide decreases vertebral and nonvertebral fractures.[22] Teriparatide is approved for the treatment of postmenopausal women with severe bone loss, men with osteoporosis who have high risk of fracture, and individuals whose condition has not improved with bisphosphonate therapy.[22] Due to an increase in the risk of osteosarcoma in growing rodents treated with high doses of teriparatide, the FDA limited the treatment duration with teriparatide to 24 months.[22] Denosumab has been shown to decrease hip, vertebral, and nonvertebral fractures compared with low doses of calcium and vitamin D.[21] Since denosumab is a biologic agent, its use is associated with elevated risk for serious infection. Denosumab can also have adverse effects on bone and calcium metabolism including hypocalcemia, atypical femoral fractures, and osteonecrosis of the jaw.[23] The recently approved osteoporosis medication, romosozumab, is a monoclonal antibody that binds to sclerostin, a regulatory bone factor in bone metabolism. The safety and efficacy of romosozumab is discussed in more depth later in this report.

The discovery of sclerostin as a key inhibitor of bone formation was made by investigators studying patients with 2 rare, genetic syndromes characterized by bone overgrowth and high bone mass; sclerosteosis and van Buchem disease.[24] Of note, individuals with sclerosteosis are resistant to bone fracture.[25] These findings stimulated interest in exploring the potential of antisclerostin therapy as a strategy to increase bone formation in patients with osteoporosis.[24] Sclerostin, a protein secreted by osteocytes, inhibits wingless-related integration (Wnt) signaling within osteoblasts thus decreasing osteoblast activity. The Wnt signaling pathway plays a significant role in skeletal development, adult skeletal homeostasis, and bone remodeling.[4] In addition, Wnt signaling is increasingly recognized for its involvement in vascular pathophysiology.[26] There is a concern that inhibition of sclerostin by romosozumab may promote or exacerbate vascular calcification.[27]

Measurement of bone density at the hip and lumbar spine with Dual X-Ray Absorptiometry (DEXA) is a surrogate marker used to diagnose osteoporosis. As well as providing diagnostic information, low BMD is recognized as a major risk factor for fractures.[28] A meta-analysis of prospective cohort studies found that every 1 SD decrease in BMD at the femoral neck in women was associated with a relative risk of 2.6 (95% CI 2.0 to 3.5) for hip fracture and 1.6 (95% CI 1.4 to 1.8) for all fractures.[29] A 1 SD decrease in lumbar spine BMD was associated with a relative risk of 2.3 (95% CI 1.9 to 2.8) for vertebral fracture and 1.5 (95% CI 1.4 to 1.7) for all fractures.[29]

Bone density monitoring via DEXA can be used to monitor the effects of pharmacologic therapy. While there are a number of approaches to monitoring therapy, there is no consensus on the optimal approach.[30] The American College of Physicians (ACP) recommends against monitoring during therapy, as many women treated with antiresorptive therapy have a reduction in fracture even when BMD does not increase.[31] In general, stability or an increase in BMD is considered to be response to osteoporosis therapy. Significant BMD loss should result in an evaluation of factors contributing to suboptimal therapeutic effect (e.g. adherence) and an assessment of alternative treatment strategies. A minimal clinically important difference has not been identified for BMD.

Osteoporosis is also diagnosed when an individual experiences a fragility fracture in a location associated with osteoporosis. A fragility fracture is a low-energy fracture that would not normally be expected to result in a broken bone, such as a fall from standing height or less. The most common fractures associated with

osteoporosis are vertebral (27%), wrist (19%), hip (14%), and pelvic (7%).[19] According to the FDA, radiographic vertebral fracture is the accepted primary endpoint for fracture trials supporting an osteoporosis indication.[27]

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:
Screening and Treatment to Prevent Osteoporotic Fractures
A high quality systematic review from the US Preventive Services Task Force evaluated recent evidence on screening and treatment to prevent osteoporotic fractures.[1] One hundred sixty-eight fair- or good-quality articles met inclusion criteria.[1] The accuracy of bone measurement tests or clinical risk assessments for identifying osteoporosis or predicting fractures varied from very poor to good.[1] Osteoporosis screening involves clinical fracture risk assessment, bone measurement testing via DEXA, or both.[1] One large, fair quality RCT comparing screening with no screening reported 28% reduction in hip fractures (2.6% vs. 3.5%; HR 0.72; 95% CI, 0.59-0.89; ARR 0.9%), but no other statistically significant benefits were observed at 5 years' follow-up (osteoporosis-related fractures, clinical fractures, or mortality).[1] This trial also assessed the effect of screening on anxiety and quality of life and found no differences between participants allocated to screening versus usual care (variance not reported , P< 0.10 for all outcomes).[1] Current evidence is insufficient to assess the balance of benefits and harms for screening for osteoporosis to prevent osteoporotic fractures in men.[1]

Moderate quality evidence showed that for women, bisphosphonates, teriparatide, raloxifene, and denosumab were associated with a lower risk of vertebral fractures compared to placebo (9 RCTs; relative risks from 0.32 to 0.64).[1] Bisphosphonates (8 RCTs, pooled RR 0.84; 95% CI 0.76-0.92) and denosumab (1 RCT, RR 0.80; 95% CI, 0.67-0.95) were associated with a lower risk of nonvertebral fractures.[1] Denosumab reduced the risk of hip fracture (1 RCT, RR 0.60; 95% CI, 0.37-0.97), but bisphosphonates did not have a statistically significant association with hip fracture reduction (3 RCTs, pooled RR 0.70; 95% CI, 0.44-1.11).[1] Absolute risk reduction was not reported. Evidence was limited for men: zoledronic acid reduced the risk of radiographic vertebral fractures (1 RCT, RR 0.33; 95% CI, 0.16-0.70); no studies demonstrated reductions in clinical or hip fractures.[1] Bisphosphonates were not consistently associated with reported harms, although rare outcomes were not generally observed in the included evidence.[1] Pooled analysis of 3 RCTs comparing raloxifene to placebo suggested a possible association of raloxifene with deep vein thrombosis, however the results were not significant (0.7% raloxifene vs. 0.3% placebo, RR 2.14; 95% CI, 0.99-4.66).[1] In summary, for women, screening to prevent osteoporotic fractures may reduce hip fractures, and treatment reduces the risk of vertebral and nonvertebral fractures. There was not consistent evidence of treatment harms.[1]

Long-Term Drug Therapy and Drug Holidays for Osteoporosis Fracture Prevention

A good quality systematic review sponsored by AHRQ summarized the effects of long-term osteoporosis drug treatment and of osteoporosis drug treatment discontinuation and holidays.[2] Long-term osteoporosis drug therapy was defined as greater than 3 years and drug holidays were defined as discontinuation for 1 year or greater after 1 year or greater of medication use.[2] Sixty-one studies were included in the systematic review. No trials compared active treatments, sequential treatments, or different durations of drug holidays.[2] In addition, harms and controls were inconsistently defined.[2]

In women with osteoporosis, 4 years of alendronate reduced clinical fractures (HR 0.64; 95% CI 0.50-0.82; Absolute Risk Reduction [ARR]=7; Number Needed to Treat [NNT]=15; moderate SOE) and radiographic vertebral fractures (HR 0.50; 95% CI 0.31-0.82; ARR 3; NNT 34; moderate SOE), while 4 years of raloxifene reduced clinical vertebral fractures (relative risk 0.58; 95% CI 0.43-0.79; ARR=2; NNT=50; high SOE), but not hip (moderate SOE) or nonvertebral fractures (high SOE). In women with osteopenia or osteoporosis, 6 years of zoledronate reduced incident clinical fractures (HR 0.73; 95% CI 0.60-0.90; ARR=5; NNT=20; moderate SOE) and clinical vertebral fractures (HR 0.41; 95% CI 0.22-0.75; moderate SOE).[2] After 3 to 5 years of prior treatment, continuation of zoledronate or alendronate versus drug holiday inconsistently reduced incident vertebral fracture outcomes (radiographic only for zoledronate [low SOE], clinical only for alendronate [moderate SOE]), but did not reduce nonvertebral fractures (low SOE).[2] Hormone therapies increased cardiovascular events, mild cognitive impairment or dementia, and other harms.[2] Observational studies showed that long-term bisphosphonates may increase atypical femoral fractures (low SOE) and osteonecrosis of the jaw compared to placebo or no treatment (low SOE in 2 comparisons, insufficient in 1).[2]

Key messages include:

- Evidence on the effects of long-term osteoporosis drug treatment and drug continuation versus discontinuation is mostly limited to white, healthy, postmenopausal women.[2]
- Long-term alendronate reduces radiographic vertebral and nonvertebral fractures in women with osteoporosis; long-term zoledronate reduces vertebral and nonvertebral fractures in women with osteopenia or osteoporosis.[2]
- Long-term bisphosphonates may increase atypical femoral fractures and osteonecrosis of the jaw, although both are rare.[2]
- In women with osteoporosis, long-term raloxifene reduces vertebral fractures, but not hip or nonvertebral fractures, and increases venous thromboembolism.[2]
- Long-term oral hormone therapies reduce hip and clinical fractures but increase multiple serious harms.[2]
- Evidence is insufficient about the effects of long-term denosumab, risedronate, ibandronate, teriparatide, and abaloparatide on fractures and harms.[2]
- Continuing bisphosphonates after 3–5 years versus discontinuation reduces some measures of vertebral fractures, but not nonvertebral fractures.[2]

Denosumab Compared To Bisphosphonates to Treat Postmenopausal Osteoporosis

A good quality systematic review and meta-analysis compared the efficacy and safety of denosumab with bisphosphonates to treat osteoporosis.[3] Eleven studies with low risk of bias involving 5446 patients (denosumab = 2873, bisphosphonates = 2573) were included in the meta-analysis.[3] The publication years ranged from 2006 to 2016. Six studies were conducted in the USA, 2 in Canada, and one each in France, Spain, the United Kingdom and Australia.[3] The dose of denosumab was 60 mg via subcutaneous injection every 6 months. Four types of bisphosphonates (alendronate, ibandronate, risedronate, and zoledronic acid) were included. The duration of follow-up ranged from 12 to 24 months. There was no significant difference between the risk of fracture (risk ratio (RR), 1.13; 95% confidence interval (CI), 0.82 to -1.55; P = 0.466), adverse events (AEs; RR 1.00; 95% CI 0.96–1.04; P = 0.957) and withdrawal due to AEs (RR 0.68; 95% CI 0.34–137; P = 0.280).[3] Current evidence suggested no benefit of denosumab for reducing risk of fracture compared to bisphosphonates.[3] More long-term follow-up RCTs are needed to identify the potential complications of denosumab.[3]

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Meta-Analysis of Romosozumab Treatment in Postmenopausal Women with Osteoporosis

Six studies were included in a high quality systematic review that was conducted to evaluate the safety and efficacy of romosozumab in the treatment of postmenopausal osteoporosis.[4] Two trials compared romosozumab with placebo, 3 trials compared romosozumab to teriparatide and 1 trial compared romosozumab to alendronate.[4] Three trials were Phase 2 studies and the other 3 were Phase 3 studies in women. Subjects were randomly assigned to receive subcutaneous (SC) injections of romosozumab 210 mg monthly for at least 12 months. Studies were graded as having low risk of bias using the Cochrane manual.[4] The meta-analysis of the trial data showed romosozumab resulted in a significantly lower risk of new vertebral fracture (RR 0.37, 95% CI 0.18–0.77, p=0.008), non-vertebral fracture (RR 0.79, 95% CI 0.68–0.92, p<0.003) and hip fracture (RR 0.59, 95% CI 0.68–0.92 p=0.002) compared with other therapies at 24 months.[4] There was no significant difference in the incidence of adverse events in patients with romosozumab compared to placebo (RR 1.00, 95% CI 0.98–1.02; p=0.93) over the 24 month study period.[4] However, more data is needed to clarify the safety of romosozumab, particularly for cardiovascular events.

After review, 5 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[33-38]

New Guidelines: No new high quality guidelines were identified.

New FDA Safety Alerts:

Table 1. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Denosumab	Prolia®	4/19	Warnings and Precautions	Hypocalcemia may be exacerbated by the use of Prolia®. Pre-existing hypocalcemia must be corrected prior to initiating therapy with Prolia®. In patients predisposed to hypocalcemia and disturbances of mineral metabolism (e.g. history of hypoparathyroidism, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, severe renal impairment [creatinine clearance < 30 mL/min] or receiving dialysis, treatment with other calcium-lowering drugs), clinical monitoring of calcium and mineral levels (phosphorus and magnesium) is highly recommended within 14 days of Prolia® injection. In some post marketing cases, hypocalcemia persisted for weeks or months and required frequent monitoring and intravenous and/or oral calcium replacement, with or without vitamin D.

Randomized Controlled Trials:

A total of 109 citations were manually reviewed from the initial literature search. After further review, 109 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION:

The humanized monoclonal antibody romosozumab was FDA-approved April 2019 for treatment of osteoporosis in postmenopausal women with a high risk of fracture.[8] Romosozumab inhibits sclerostin, a protein secreted by osteocytes that blocks bone formation. As a result of romosozumab administration, bone formation is increased and bone resorption decreased. One 210 mg dose of romosozumab consists of two (105 mg) injections, one immediately following the other, given once a month by a health care professional.[8] Duration of romosozumab therapy is limited to 1 year because the bone-forming effect of the drug wanes after 12 doses.[8]

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:

The safety and efficacy of romosozumab were evaluated in 3 clinical trials involving women with postmenopausal osteoporosis and 1 trial in older men with previous fracture. FDA approval for romosozumab was based on 2 large Phase 3 trials, FRAME and ARCH.[27] The good quality FRAME trial was an international, randomized, double blind study in 7180 women with an average age of 71 years and mean T score at femoral neck of -2.7.[5] A small percentage (18%) of subjects had previous vertebral fracture at baseline.[5] Subjects received either romosozumab 210 mg subcutaneously (SC) once a month or placebo for 12 months followed by an additional 12 months of open label therapy with denosumab 60 mg SC every 6 months (to preserve the BMD gains with romosozumab) in both treatment groups.[5] All participants received daily calcium 500-1,000 mg and vitamin D 600-800 International Unit (IU) supplementation. The co-primary endpoints were the proportion of subjects with new vertebral fractures at 12 and 24 months.[5] Secondary end points included clinical (a composite of nonvertebral and symptomatic vertebral) fractures and nonvertebral fractures.[5] During the first 12 months of therapy, romosozumab significantly reduced the incidence of new vertebral fractures compared to placebo (0.5% with romosozumab vs. 1.8% with placebo; RR 0.27; 95% CI, 0.16 to 0.47; P<0.001; ARR 1.3%; NNT 77).[5] At 24 months, the rates of vertebral fractures remained lower in the romosozumab group than in the placebo group after each group made the transition to denosumab (0.6% in the romosozumab group vs. 2.5% in the placebo group, RR 0.75; 95% CI, 0.16 to 0.40; P<0.001; ARR 1.9%; NNT 53).[5] However, the reduction in non-vertebral fractures at 12 months was not statistically significant (1.6% with romosozumab vs. 2.1% with placebo; P=0.10; 95% CI, 0.53 to 1.05).[5]

The good quality ARCH study compared the effects of romosozumab 210 mg SC once monthly with oral alendronate 70 mg once weekly for 12 months, followed by open label alendronate therapy in both treatment groups for up to an additional 2 years.[6] A total of 4093 women were enrolled in this study. The women enrolled in this trial were at much higher risk of fracture than the women in the placebo-controlled FRAME study. The average age of the study participants was 74 years, and more than half of the women were age 75 or older. Ninety-nine percent of the women had a history of a fragility fracture.[6] The co-primary endpoints of the study were the reduction in new vertebral fracture incidence at 24 months and the cumulative incidence of clinical fracture through the primary analysis period.[6] The primary analysis period ended when at least 330 subjects had a clinical fracture and all subjects had completed the 24-month visit; median time on study at time of primary analysis was 33 months.[6] Secondary endpoints included nonvertebral and hip fracture risk reduction at 24 months. After 24 months of therapy, new vertebral fractures occurred in 6.2% of the women who received romosozumab and in 11.9% of alendronate-treated women (RR 0.52; 95% CI, 0.40 to 0.66; P<0.001; ARR 5.7%; NNT 18).[6] Clinical (nonvertebral and symptomatic vertebral) fractures occurred in 9.7% of subjects in the romosozumab-to-alendronate group versus 13.0% in the alendronate-to-alendronate group, representing lower risk clinical fracture with romosozumab (RR 0.73; 95 CI 0.61 to 0.88; <0.001; ARR 3.3%; NNT 31).[6]

The fair quality STRUCTURE trial compared the effects of 12 months of romosozumab with teriparatide in women who were transitioning from bisphosphonate therapy.[39] Previous data suggest that the clinical benefit of teriparatide might be reduced in patients transitioning from bisphosphonates compared with bisphosphonate-naive patients.[39] This trial was a randomized, open-label assessment conducted in 436 postmenopausal women with osteoporosis at high risk for fracture.[39] The average age of subjects was 72 years and all the participants had experienced a previous fracture. The open-label study design was necessary due to the inability to mask the teriparatide pen. The primary endpoint was percentage change from baseline in total hip BMD after 12 months of therapy. The mean percentage change from baseline in total hip BMD was 2.6% in the romosozumab group and - 0.6% in the women who received teriparatide (mean difference (MD) 3.2%; 95% CI, 2.7 to 3.8; p<0.0001).[39] Fracture incidence, the primary endpoint recommended by the FDA for osteoporosis trials, was not evaluated in this trial. The findings from this trial suggest that romosozumab might be an effective treatment option for patients at increased risk for fracture who are transitioning from oral bisphosphonate therapy.[39]

The fair quality BRIDGE trial was a placebo-controlled study conducted in 245 men with a history of fracture.[7] Subjects were randomized 2:1 to receive romosozumab 210 mg SC monthly or placebo for 12 months. The primary efficacy endpoint was percentage change from baseline in lumbar spine BMD at month 12. After 12 months of therapy, the mean percentage change from baseline in the lumbar spine BMD was significantly greater for the romosozumab group than for the placebo group (12.1% vs 1.2% respectively; P < 0.001; 95% CI not reported).[7] Fracture incidence was not evaluated in this trial. Currently, romosozumab does not have FDA approval for use in men. More details about the study design of all 4 trials is summarized in **Table 5.**

Study Limitations:

The study population in the FRAME trial was not representative of the US population (only about 3% North American while about 40% were Latin American).[5] A total of 132 patients (1.8%) were from the United States. In addition, this study noted lower rates of non-vertebral fracture and lower FRAX scores in Latin American regions, which may have underestimated the non-vertebral rate in the placebo group.[27] The investigator attributes the lack of significance of the nonvertebral fracture reduction to a regional subgroup interaction in Central/Latin America where a lower than expected nonvertebral fracture rate in the placebo group was observed (assumed 3.5%, observed 1.2%).[27] The observed nonvertebral fracture rate was also lower than expected in the small enrolled population in North America (assumed 3.5%, observed 1.1%).[27] Thirdly, although romosozumab treatment decreased drastically the risk of vertebral fractures at 12 months, reductions of similar magnitude (61–65%) in such fractures have already been described after 1 year of treatment with anti-resorptive agents.[40] Finally, the 25% reduction in the incidence of nonvertebral fractures observed after 1 year of treatment with romosozumab, although clinically relevant, was not statistically significant.[40]

The FDA noted that reduction of clinical fractures is not an appropriate endpoint in the FRAME and ARCH trials because the term, clinical fracture, does not have clinical meaningfulness among healthcare professionals and can be subject to different interpretation in the labeling.[27] In addition, clinical fracture rates in the FRAME study are combined from nonvertebral fractures (85%) and clinical vertebral fractures (15%).[27] As nonvertebral fracture endpoints were not statistically significant, the incidence rate differences for clinical fractures in the romosozumab group compared to placebo are from clinical vertebral fractures which were already counted in the primary endpoint.[27]

A limitation of the STRUCTURE trial was the open-label study design, which was necessary because of the inability to mask the teriparatide pen. Although the treatment assignments were open label, the efficacy endpoints were objective measurements and assessed by investigators who were masked to treatment allocation.[39] Also, this study was not powered to assess the difference in fracture incidence between treatment groups, and fracture events were not adjudicated or confirmed.[39] Efficacy endpoints in the BRIDGE trial were intermediate (BMD changes) and did not include study fracture incidence after therapy in men.[27]

Clinical Safety:
In the FRAME trial, the incidence of nonfatal serious adverse events was 8.7% in the placebo group and 9.6% in the romosozumab group.[5] The most common adverse reactions reported with romosozumab (greater than or equal to 5% and at a higher incidence than placebo) were arthralgia and headache in both the FRAME and ARCH trials.[5] The most common adverse reaction leading to discontinuation of romosozumab was arthralgia (6 subjects [0.2%] in the placebo group and 5 subjects [0.1%] in the romosozumab group).[5] In the ARCH trial, the incidence of nonfatal serious adverse events was 13.3% in the alendronate group and 11.9% in the romosozumab group.[6] The percentage of patients who withdrew from the study due to adverse events was 1.2% in the alendronate group and 1.2% in the romosozumab group.[6] Adverse reactions occurring in greater than 2% of women treated with romosozumab compared to placebo are presented in **Table 3.**

Table 3. Adverse reactions occurring in ≥ 2% of romosozumab-treated women compared to placebo[8]

Adverse Reaction	Placebo	Romosozumab
Arthralgia	434 (12.1%)	468 (13.1%)
Headache	208 (5.8%)	235 (6.6%)
Muscle Spasms	140 (3.9%)	163 (4.6%)
Edema	67 (1.9%)	86 (2.4%)
Asthenia	79 (2.2%)	84 (2.3%)
Neck Pain	54 (1.5%)	80 (2.2%)
Insomnia	68 (1.9%)	72 (2.0%)
Paresthesia	62 (1.7%)	72 (2.0%)

The immunogenicity of romosozumab was evaluated using an immunoassay for the detection of anti-romosozumab antibodies.[8] Antibody formation against romosozumab occurred in 20% of patients on romosozumab and neutralizing capability occurred in 5% of patients with binding antibodies.[27] The presence of antibodies can reduce romosozumab exposure but do not appear to affect the effectiveness of romosozumab.[27]

Severe adverse events observed during clinical trials included osteonecrosis of the jaw (< 1%) and atypical fracture (<1%).[8] In the ARCH trial, serious cardiovascular events were observed more often with romosozumab than with alendronate (50 of 2,040 patients (2.5%) compared with 38 of 2,014 patients (1.9%); OR 1.31; 95% CI 0.85–2.00).[6] Sixteen patients (0.8%) treated with romosozumab had cardiac ischemic events compared with six (0.3%) treated with alendronate (OR 2.65; 95% CI 1.03–6.77).[6] Based on this data, the romosozumab drug label has a black box warning regarding the possibility for increased risk of myocardial infarction, stroke and cardiovascular death associated with romosozumab adminstration.[8] Romosozumab should not be initiated in patients who have had a myocardial infarction or stroke within the preceding year.[8] If a patient experiences a myocardial infarction or stroke during therapy, romosozumab should be discontinued.[8]

Notably, the FRAME trial did not identify any imbalance in cardiovascular events in the romosozumab compared with the placebo groups.[5] The differences in adverse effects may be due to differences in the patient populations studied in the FRAME and ARCH trial. Women in the ARCH study were, on average, 4 years older than those enrolled in the FRAME trial. In addition, 96% of women in the ARCH trial had a prevalent vertebral fracture compared with only 18% of women in the FRAME trial. As osteoporotic fractures are associated with other ageing co‑morbidities, including cardiovascular disease, women in the ARCH trial may have been less healthy than the women in the FRAME trial.[27]

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

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Percentage of patients with new vertebral fractures
2) Percentage of patients with new non-vertebral fractures
3) Serious adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Percentage of patients with new vertebral fractures at 12 and 24 months

Table 4. Pharmacology and Pharmacokinetic Properties.[8]

Parameter	
Mechanism of Action	Sclerostin inhibitor which increases bone formation
Bioavailability	81%
Distribution	Volume of distribution: 3.92 Liters
Elimination	Monoclonal antibody unlikely to be filtered by the kidney or excreted in urine
Half-Life	12.8 days after 3 doses every 4 weeks
Metabolism	Metabolic pathway has not been characterized

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. Cosman F, et al.[5] FRAME Phase 3 RCT, DB, PC, MC, PG N=7180	1. Romosozumab 210 mg SC monthly for 12 months followed by OL denosumab 60 mg SC every 6 months for 12 months 2. Placebo SC monthly for 12 months followed by OL denosumab 60mg SC every 6 months for 12 months	Demographics: 1. Mean age: 71 yo 2. Mean T-score at lumbar spine and femoral neck: -2.7 3. Previous vertebral fracture at baseline: 18% 4. Previous nonvertebral fracture: 22% 5. Ethnic group: -Hispanic 40% -Non-Hispanic 60% Key Inclusion Criteria: 1. Ambulatory, postmenopausal women aged 55 to 90 yo 2. Total hip or femoral neck BMD T-score between -2.5 and -3.5 Key Exclusion Criteria: 1. Total hip or femoral neck T-score ≤ 3.5 2. Previous hip fracture or more than 2 vertebral fractures 3. History of metabolic bone disease 4. Osteonecrosis of the jaw 5. Vitamin D level < 20 ng/ml 6. Current use of medications that affect bone metabolism	ITT: 1. 3589 2. 3591 PP: (completed 12-mo DB period) 1. 3185 2. 3205 Attrition: 12 mos- 1. 404 (11%) 2. 386 (11%) 24 mos- 1. 595 (17%) 2. 559 (16%)	Co-Primary Endpoints: 1. Percentage of patients with new vertebral fractures at 12 mos 1. 16 (0.5%) 2. 59 (1.8%) RR 0.27 (95% CI 0.16 to 0.47) P<0.001 2. Percentage of patients with new vertebral fractures at 24 mos 1. 21 (0.6%) 2. 84 (2.5%) RR 0.25 (95% CI 0.16 to 0.40) P<0.001 Secondary Endpoints: 1. Percentage of patients with new nonvertebral fractures at 12 mos 1. 56 (1.6%) 2. 75 (2.1%) HR 0.75 (95% CI 0.53 to 1.05) p=0.10 2. Percentage of patients with new nonvertebral fractures at 24 mos 1. 96 (2.7%) 2. 129 (3.6%) HR 0.75 (95% CI 0.57 to 0.97) p=0.06	1.3%/77 1.9%/53 NS NS	TEAEs at 12 mos 1. 2806 (78.4%) 2. 2850 (79.7%) SAEs at 12 mos 1. 344 (9.6%) 2. 312 (8.7%) Drug discontinuation due to AE at 12 mos 1. 103 (2.9%) 2. 94 (2.6%) Injection Site Reactions 1. 187 (5.1%) 2. 104 (2.9%) CV events 1. 46 (1.3%) 2. 46 (1.3%) Death 1. 29 (0.8%) 2. 23 (0.6%) 95% CI and p value NR for all		**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1 via IVRS. Stratified by age (<75, ≥75yo) and prevalent vertebral fracture. Baseline characteristics similar in both arms. Performance Bias: Low. Placebo presented in identical containers and stored/packaged the same as romosozumab. Detection Bias: Low. Patients, investigators, and sponsors blinded to initial treatment assignment. Central radiologic facility used for fracture assessment, DEXA and CT readings. Radiologists unaware of treatment assignments. Attrition Bias: Low. Similar attrition rates in both arms noted at 12 and 24 months. Reasons for discontinuation were similar in both arms. ITT analysis used to assess treatment effect. Multiple-imputation approach used to handle missing data. Reporting Bias: Low. Protocol available online. Other Bias: Unclear. Amgen and UCB Pharm designed the trial and Amgen was responsible for trial oversight. Several authors received grant support from Amgen. **Applicability**: Patient: The study population was not representative of the US population in postmenopausal women with osteoporosis. Small percentage of subjects had previous vertebral fracture at baseline. Intervention: Romosozumab dose was proven to be efficacious in Phase 2 trial. Comparator: Would be more informative to compare romosozumab with bisphosphonate. Outcomes: Cumulative incidence of new vertebral fractures is a reasonable endpoint to assess treatment effect. Setting: 222 centers in 25 countries: Central/Latin America: 43% Central/Eastern Europe: 29% Western Europe, Australia, New Zealand: 14% Asia/Pacific: 12% North America: 3%

2. Saag KG, et al.[41] ARCH trial Phase 3 RCT, DB, MC N=4093	1. Romosozumab 210 mg SC once monthly for 12 months followed by OL alendronate 70 mg orally once weekly 2. Alendronate 70 mg orally once weekly followed by OL alendronate 70 mg orally once weekly	Demographics: 1. Mean age: 74 yo 2. Mean T-scores: -Lumbar spine: -2.96 -Total hip: -2.80 -Femoral neck: -2.90 3. Ethnic group: -Non-Hispanic: 68 % -Hispanic: > 32% 4. Previous fracture: 99% Key Inclusion Criteria: 1. Postmenopausal women aged 55 to 90 yo with total hip or femoral neck BMD T-score ≤ -2.5 and at least one moderate or severe vertebral fracture OR T-score ≤ -2.0 with either ≥ 2 moderate to severe vertebral fractures or a fracture of the proximal femur 3-24 mos before randomization Key Exclusion Criteria: 1. Severe metabolic or bone disease 2. Current use of bone metabolism agents 3. Cr Cl < 35 ml/min	ITT: 1. 2046 2. 2047 PP: (completed study through primary analysis) 1. 1574 2. 1576 Attrition at 12 mos: 1. 215 (11%) 2. 224 (11%)	Co-primary Endpoints: 1. Cumulative incidence of new vertebral fracture at 24 months 1. 127 (6.2%) 2. 243 (11.9%) RR 0.50 (95% CI, 0.40 to 0.66), P<0.001 2.Cumulative incidence of new clinical (nonvertebral fracture and clinical vertebral fracture) fracture through primary analysis period (> 24 mos) 1. 198 (9.7%) 2. 266 (13%) HR 0.73 (95% CI 0.61 to 0.88), P<0.001 Secondary Endpoints: 1. Cumulative incidence of new vertebral fracture at 12 months 1. 82 (4.0%) 2. 128 (6.3%) RR 0.63 (95% CI, 0.47 to 0.85), P=0.003 2. Incidence of nonvertebral fracture at 12 months 1. 70 (3.4%) 2. 95 (4.6%) RR 0.74 (95% CI 0.54 to 1.01) P=0.057 3. Incidence of hip fracture at 12 months 1. 14 (0.7%) 2. 22 (1.1%) RR 0.64 (95% CI 0.3 to 1.26 P=0.19	5.7%/18 3.3%/31 2.3%/44 NS NS	TEAEs at 12 mos 1. 1544 (76%) 2. 1584 (79%) SAEs at 12 mos 1. 262 (13%) 2. 278 (14%) SAEs leading to drug discontinuation at 12 mos 1. 70 (3.4%) 2. 64 (3.2%) Injection Site Reaction at 12 mos 1. 90 (4.4%) 2. 53 (2.6%) Death 1.30 (1.5%) 2. 21 (1.0%) CV Events at 12 mos 1. 50 (2.5%) 2. 38 (1.9%) OR 1.31 (95% CI 0.85 to 2.00) P value and 95% CI NR for all		**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1 via IVRS. Stratified according age (<75 yo vs. ≥75 yo). Baseline demographics balanced between groups. Performance Bias: Low. Subjects received a matched oral placebo or matched subcutaneous placebo depending on treatment assignment to maintain blinding. Detection Bias: Low. Patients, outcome assessors, health care providers, data collectors, and data analysts blinded to treatment assignment. All DEXA scan data submitted electronically to the central imaging vendor for analysis. Attrition Bias: Low. 11% of subjects withdrew from the trial, reasons for discontinuation were similar in both arms. ITT analysis used to assess treatment effect. Multiple imputation used for missing fracture status. Reporting Bias: Low. Protocol available online Other Bias: Unclear. Funded by Amgen. Amgen and UCB Pharma designed the trial, and Amgen was responsible for trial oversight and data analyses per a prespecified statistical analysis plan. An external independent data monitoring committee monitored unblinded safety data. **Applicability**: Patient: Women at high risk for fracture were included in the trial – 99% of subjects had a previous fracture. Intervention: Romosozumab dose evaluated in Phase 2 trials. Comparator: Bisphosphonate therapy is standard of care to manage osteoporosis. Outcomes: Incidence of vertebral fracture is an established endpoint for evaluating osteoporosis therapy. Setting: 125 centers: Central or Eastern Europe: 40% Latin America: 34% Western Europe, Australia, New Zealand: 13% Asia-Pacific or South Africa: 11% North America: 2%

3. Langdahl BL, et al.[39] STRUCTURE trial Phase 3 trial, OL, MC, PG N=436	1. Romosozumab 210 mg SC once monthly 2. Teriparatide 20 mcg SC once daily	Demographics: 1. Mean age: 72 yo 2. Mean baseline BMD T-score: -Total hip: -2.2 -Lumbar spine -2.9 -Femoral neck -2.4 3. Average duration of bisphosphonate therapy: 6.2 years 4. Ethnic group: -White: 89% -Other: 11% 5. Previous fracture: 100% Key Inclusion Criteria: 1. Ambulatory, postmenopausal women aged 55 to 90 yo with osteoporosis (T-score ≤ -2.5 at total hip, lumbar spine, femoral neck) and history of fracture after age 50 previously treated with bisphosphonate therapy for minimum of 3 years Key Exclusion Criteria: 1. Use of osteoporosis agents other than bisphosphonates 2. Vitamin D level < 50 nmol/L 3. History of metabolic or bone disease 4. Hyper- or hypocalcemia 5. Uncontrolled hyper- or hypothyroidism	ITT: 1. 218 2. 218 PP: 1. 198 2. 200 Attrition: 1. 20 (9%) 2. 18 (8%)	Primary Endpoint: Mean percentage change from baseline in total hip BMD at 12 months 1. 2.6% 2. -0.6% MD 3.2% (95% CI 2.7 to 3.8) p<0.0001 Secondary Endpoints: 1. Percent change from baseline in femoral neck BMD at 12 months 1. 3.2% 2. -0.2% MD 3.4% (95% CI NR) p<0.0001 2. Percent change from baseline in lumbar spine BMD at 12 months 1. 9.8% 2. 5.4% MD 4.4% (95% CI NR) p<0.0001	NA NA NA	SAEs 1. 17 (8%) 2. 23 (11%) SAEs leading to drug discontinuation 1. 6 (3%) 2. 12 (6%) Hypercalcemia 1. 2 (<1%) 2. 22 (10%) Arthralgia 1. 22 (10%) 2. 13 (6%) Injection Site Reaction 1. 17 (8%) 2. 6 (3%) Death 1. 1 (< 1%) 2. 1 (< 1%) P value and 95% CI NR		**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1 via IVRS. Baseline demographics similar in both treatment groups. Performance Bias: High. Open label study due to inability to conceal teriparatide pen formulation. Patients assigned to teriparatide self-injected the study medication while patients assigned to romosozumab were administered the medication by HCPs. Detection Bias: Unclear. Investigators assessing efficacy endpoints were masked to treatment assignment. Attrition Bias: Low. Similar rates of study withdrawal in both arms with similar reasons for discontinuation. Reporting Bias: Low. Protocol is available at European Clinical Trial Register. Other Bias: Unclear. Funded by Amgen, Astellas, and UCB Pharma. Amgen and UCB Pharma designed the study in collaboration with external investigators. Amgen was responsible for study monitoring, oversight, and statistical analysis. A significant percentage of contributing authors received financial support from Amgen or were employed by Amgen. **Applicability**: Patient: Patients at high risk for fracture; primarily European, exposed to bisphosphonate therapy for 3 years with history of fracture. Intervention: Dose of romosozumab evaluated in Phase 2 trials Comparator: Teriparatide is a bone forming agent with a different MOA from romosozumab. Clinical benefit of teriparatide may be reduced by prior bisphosphonate therapy. Outcomes: Efficacy endpoints were intermediate (BMD changes) and did not include study fracture incidence after therapy due to inadequate power to assess differences in fracture rate. Setting: 46 sites in North America (7%), Latin America (18%), and Europe (75%)

4. Lewiecki EM, et al.[7] BRIDGE trial Phase 3 RCT, MC, DB, PC N=245	1. Romosozumab 210 mg SC once monthly for 12 months 2. Placebo SC once monthly for 12 months	Demographics: 1. Mean age: 72 yo 2. Baseline lumbar spine T-score: -2.3 3. Previous fracture: 54% 4. Ethnic group: White: 74% Asian: 11% Other: 15% Key Inclusion Criteria: 1.Men aged 55 to 90 yo with T-score ≤ -2.5 at the spine or hip or ≤ 1.5 at the spine or hip with a history of nonvertebral or vertebral fractures after age 45 Key Exclusion Criteria: 1. T-score ≤ -3.50 at the hip 2. History of hip fracture 3. History of metabolic or bone disease 4. Current use of medications that affect bone metabolism	ITT: 1. 163 2. 82 PP: 1. 152 2. 79 Attrition: 1. 11 (7%) 2. 3 (4%)	Primary Endpoint: Percent changes from baseline in lumbar spine BMD at 12 months 1. 12.1% 2. 1.2% P<0.001 95% CI NR Secondary Endpoints: 1. Percent change from baseline in DXA BMD at total hip at 12 months 1. 2.5% 2. -0.5% P<0.001 95% CI NR 2. Percent change from baseline in DXA BMD at femoral neck at 12 months 1. 2.2% 2. -0.2% P<0.001 95% CI NR	NA NA NA	TEAEs at 12 mos 1. 123 (76%) 2. 65 (80%) SAEs 1. 21 (12.9%) 2. 10 (12.3%) SAE leading to drug discontinuation 1. 5 (3.1%) 2. 1 (1.2%) Injection Site Reactions 1. 9 (5.5%) 2. 3 (3.7%) CV events 1. 8 (4.9%) 2. 2 (2.5%) p-value and 95% CI NR for all		**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 2:1 to receive romosozumab or placebo via IVRS. Stratified by geographic region. Baseline demographics balanced between groups. Performance Bias: Low. Matched placebo given to subjects in the placebo arm. Detection Bias: Low. BMD measurements analyzed by a central imaging vendor. Attrition Bias: Low. Similar attrition rates in both arms. Reporting Bias: Low. Protocol available at ClinicalTrials.gov Other Bias: Unclear. Amgen Inc., UCB Pharma and Astellas Pharma provided financial support for this trial. The authors all report grant support from Amgen and UCB Pharma. **Applicability**: Patient: Primarily studied in Europe (66%) with relatively few participants in North America (9%). Applies to older men with 54% having a previous fracture. Intervention: Modeled after FRAME trial, as Phase 2 trials did not include men. Comparator: Would be more informative to compare romosozumab to standard of care (bisphosphonate) approved to treat osteoporosis in men. Outcomes: Efficacy endpoints were intermediate (BMD changes) and did not include study fracture incidence. Setting: 31 centers in Europe (66%), Latin America (14%), Japan (11%) and North America (9%)

Abbreviations [alphabetical order]: ARR = absolute risk reduction; BMD = bone mineral density; CI = confidence interval; CV = cardiovascular; DB = double blind; DEXA = dual-energy x-ray absorptiometry; HCP = health care professional; HR = hazard ratio; ITT = intention to treat; IVRS = interactive voice-response system; MC = multi-center; MD = mean difference; mITT = modified intention to treat; MOA = mechanism of action; Mos = months; N = number of subjects; NA = not applicable; NNH = number needed to harm; NR = not reported; NNT = number needed to treat; OL = open label; OR = odds ratio; PC = placebo controlled; PG = parallel group; PP = per protocol; RCT = randomized clinical trial; RR = risk ratio; SAE = serious adverse event; SC = subcutaneous; SEAs = serious adverse effects; TEAE = treatment emergent adverse effects; YO = years old

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
alendronate sodium	ALENDRONATE SODIUM	TABLET	PO	Y
alendronate sodium	FOSAMAX	TABLET	PO	Y
ibandronate sodium	BONIVA	TABLET	PO	Y
ibandronate sodium	IBANDRONATE SODIUM	TABLET	PO	Y
risedronate sodium	ACTONEL	TABLET	PO	Y
risedronate sodium	RISEDRONATE SODIUM	TABLET	PO	Y
abaloparatide	TYMLOS	PEN INJCTR	SQ	N
alendronate sodium	ALENDRONATE SODIUM	SOLUTION	PO	N
alendronate sodium	BINOSTO	TABLET EFF	PO	N
alendronate sodium/vitamin D3	FOSAMAX PLUS D	TABLET	PO	N
calcitonin,salmon,synthetic	CALCITONIN-SALMON	SPRAY/PUMP	NS	N
calcitonin,salmon,synthetic	MIACALCIN	VIAL	IJ	N
denosumab	PROLIA	SYRINGE	SQ	N
etidronate disodium	ETIDRONATE DISODIUM	TABLET	PO	N
ibandronate sodium	BONIVA	SYRINGE	IV	N
ibandronate sodium	IBANDRONATE SODIUM	SYRINGE	IV	N
raloxifene HCl	EVISTA	TABLET	PO	N
raloxifene HCl	RALOXIFENE HCL	TABLET	PO	N
risedronate sodium	ATELVIA	TABLET DR	PO	N
risedronate sodium	RISEDRONATE SODIUM DR	TABLET DR	PO	N
teriparatide	FORTEO	PEN INJCTR	SQ	N
denosumab	XGEVA	VIAL	SQ	
ibandronate sodium	IBANDRONATE SODIUM	VIAL	IV	
pamidronate disodium	PAMIDRONATE DISODIUM	VIAL	IV	
zoledronic ac/mannitol/0.9NaCl	ZOLEDRONIC ACID	PIGGYBACK	IV	
zoledronic acid	ZOLEDRONIC ACID	VIAL	IV	
zoledronic acid	ZOMETA	VIAL	IV	
zoledronic acid/mannitol-water	RECLAST	PGGYBK BTL	IV	
zoledronic acid/mannitol-water	ZOLEDRONIC ACID	PGGYBK BTL	IV	
zoledronic acid/mannitol-water	ZOMETA	PGGYBK BTL	IV	
zoledronic acid/mannitol-water	ZOLEDRONIC ACID	PIGGYBACK	IV	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to May Week 3 2019, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to May 23, 2019

1.	Paget Disease, Extramammary/ or Pagets disease.mp.	6843
2.	Osteoporosis, Postmenopausal/ or Osteoporosis/ or osteoporosis.mp.	73213
3.	Risedronate Sodium/	1146
4.	Alendronate/	3547
5.	ibandronate.mp.	869
6.	Etidronic Acid/	2714
7.	calcitonin/	15604
8.	Raloxifene Hydrochloride/	2560
9.	Teriparatide/	1813
10.	Denosumab/	1364
11.	Zoledronic acid.mp.	3905
12.	Pamidronate.mp.	2816
13.	Abaloparatide.mp	53
14.	Romosozumab	90
15.	1 or 2	79425
16.	3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	32101
17.	limit 16 to (english language and humans and yr="2018 -Current" and (clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta-analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review"))	109

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

EVENITY™ (romosozumab-aqqg) injection, for subcutaneous use
Initial U.S. Approval: 2019

WARNING: POTENTIAL RISK OF MYOCARDIAL INFARCTION, STROKE AND CARDIOVASCULAR DEATH
See full prescribing information for complete boxed warning.

- **EVENITY may increase the risk of myocardial infarction, stroke and cardiovascular death. (5.1)**
- **EVENITY should not be initiated in patients who have had a myocardial infarction or stroke within the preceding year. Consider whether the benefits outweigh the risks in patients with other cardiovascular risk factors. (5.1)**
- **If a patient experiences a myocardial infarction or stroke during therapy, EVENITY should be discontinued. (5.1)**

----------INDICATIONS AND USAGE----------
EVENITY is a sclerostin inhibitor indicated for the treatment of osteoporosis in postmenopausal women at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. (1)

Limitations of Use: Limit duration of use to 12 monthly doses. If osteoporosis therapy remains warranted, continued therapy with an anti-resorptive agent should be considered. (1.2)

----------DOSAGE AND ADMINISTRATION----------
- Two separate subcutaneous injections are needed to administer the total dose of 210 mg. Inject two syringes, one after the other. (2.1)
- Should be administered by a healthcare provider. (2.1)
- Administer 210 mg subcutaneously once every month for 12 doses in the abdomen, thigh, or upper arm. (2.2)
- Adequately supplement calcium and vitamin D during treatment. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 105 mg/1.17 mL solution in a single-use prefilled syringe. A full dose of EVENITY requires two single-use prefilled syringes. (3)

----------CONTRAINDICATIONS----------
- Hypocalcemia (4)
- Known hypersensitivity to EVENITY (4)

----------WARNINGS AND PRECAUTIONS----------
- Major Adverse Cardiac Events (MACE): Monitor for symptoms of MI and stroke and seek prompt medical attention if symptoms occur. (5.1)
- Hypersensitivity: Hypersensitivity reactions, including angioedema, erythema multiforme, dermatitis, rash, and urticaria. Discontinue EVENITY if a clinically significant allergic reaction occurs. (5.2)
- Hypocalcemia: Adequately supplement calcium and vitamin D during treatment with EVENITY. (5.3)
- Osteonecrosis of the Jaw: Monitor for symptoms. Consider discontinuation of therapy based on benefit-risk assessment. (5.4)
- Atypical Femoral Fracture: Evaluate new or unusual thigh, hip, or groin pain to rule out an incomplete femur fracture. (5.5)

----------ADVERSE REACTIONS----------
The most common adverse reactions (≥ 5%) reported with EVENITY in clinical trials were arthralgia and headache. (6.1)

----------USE IN SPECIFIC POPULATIONS----------
Renal Impairment: Patients with severe renal impairment or receiving dialysis are at greater risk of developing hypocalcemia. Monitor serum calcium and supplement with calcium and vitamin D. (5.3, 8.7)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Inc. at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 04/2019

Appendix 4: Key Inclusion Criteria

Population	Post-menopausal women at risk for fracture (Total hip or femoral neck T-score between -2.5 and -3.5)
Intervention	Romosozumab 210 mg SC once a month for 12 months
Comparator	Placebo, teriparatide, alendronate
Outcomes	Percentage of women experiencing new vertebral fracture
Timing	1-2 years
Setting	Primarily Europe and Latin America

Bone Metabolism Agents

Goal(s):

To ensure appropriate drug use and safety of bone metabolism ~~resorption suppression~~ agents by authorizing utilization in specified patient populations.

Length of Authorization:

- 12 to 24 months

Requires PA:

Non-preferred drugs

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an OHP-funded condition?	**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? Note: • Preferred products do not require a PA. • 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	**No:** Go to #4

Approval Criteria		
4. Has the patient tried and failed an oral bisphosphonate (alendronate, risedronate, or ibandronate) or do they have contraindications to these treatments? (document contraindication, if any)	**Yes:** Go to #5	**No:** Pass to RPh; deny and recommend trial of oral bisphosphonate
5. Is the request for raloxifene?	**Yes:** Go to #6	**No:** Go to #7
6. Is the patient pregnant and/or at increased risk for thromboembolism or stroke?	**Yes:** Pass to RPh. Deny; medical appropriateness. Note: inform prescriber of pregnancy category X and boxed warning for venous thromboembolism and stroke.	**No:** Approve for up to 12 months
7. Is the request for teriparatide and is the patient at high risk for fracture? Examples include: • Postmenopausal women with osteoporosis and T-score ≤ - 2.5 or history of fracture • Men with primary or hypogonadal osteoporosis* • Men or women with osteoporosis associated with sustained systemic glucocorticoid therapy	**Yes:** Go to #10	**No:** Go to #8

Approval Criteria		
8. Is the request for abaloparatide and is the patient a postmenopausal woman aged 49 to 86 years with osteoporosis at high risk for fracture? Inclusion criteria from the ACTIVE[1] trial: • Women with T score between - 2.5 and -5.0 AND radiologic evidence of vertebral fracture or history of nonvertebral fracture within the past 5 years OR • Women aged 65 years or older with T score between -3.0 and -5.0 without history of fracture OR T score between -2.0 and 5.0 with history of fracture.	**Yes:** Go to #9	**No:** Go to #11
9. Has the patient received treatment with anticonvulsants that affect Vitamin D metabolism (phenobarbital, phenytoin, carbamazepine or primidone) or with chronic heparin within the past 6 months OR has the patient received daily treatment with oral, intranasal, or inhaled corticosteroids in the past 12 months?	**Yes:** Pass to RPh. Deny; medical appropriateness. (These patients were excluded from the ACTIVE[1] trial)	**No:** Go to #10.
10. Does the patient meet one of the following conditions: • Concomitant bisphosphonate; or • Pediatric or young adult with open epiphyses; or • History of osteosarcoma or skeletal malignancies; or • Metabolic bone disease; or • Underlying hypercalcemic disorders; or • Unexplained elevated alkaline phosphatase levels?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for up to 24 months (depending on when therapy was initiated. Teriparatide and abaloparatide are only FDA approved for a total duration of therapy of 2 years.)
11. Is the request for romosozumab and is the patient a postmenopausal women with osteoporosis and T-score ≤ -2.5 or history of fracture?	**Yes:** Go to # 12	**No:** Go to # 13

Approval Criteria		
12. Has the patient had a myocardial infarction or stroke within the past year?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for up to 12 months maximum.* *Note: FDA has only approved use of romosozumab for a total of 12 months. If continued osteoporosis therapy is warranted, continue therapy with an anti-resorptive agent (e.g. bisphosphonates, denosumab, or raloxifene).
13. RPh only: All other indications need to be evaluated as to whether they are funded by the OHP or not.	If funded and clinic provides supporting literature, approve for up to 12 months	If non-funded, deny; not funded by the OHP

P&T Review: *7/19 (DM); 3/18; 7/16; 9/10*
Implementation: *TBD; 4/16/18; 8/16, 1/1/11*

** FDA approved osteoporosis treatments for men include alendronate, risedronate, zoledronic acid, teriparatide, and denosumab.*

1. Miller PD, Hattersley G, Riis BJ, et al. Effect of Abaloparatide vs Placebo on New Vertebral Fractures in Postmenopausal Women With Osteoporosis: A Randomized Clinical Trial. JAMA.316 (7):722-733.

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

New Drug Evaluation: Aemcolo™ (rifamycin) delayed release tablet, oral

Date of Review: July 2019
Generic Name: rifamycin

End Date of Literature Search: December 2018
Brand Name (Manufacturer): Aemcolo™ (Cosmo Technologies, Ltd)
Dossier Received: no

Research Questions:

1. What is the efficacy of rifamycin compared to placebo or currently available therapy for the treatment of adults with travelers' diarrhea (TD)?
2. Is rifamycin safer than alternative treatments for TD?
3. Are there any subgroups (based on age, ethnicity, comorbidities, disease duration or severity) that would particularly benefit or be harmed from treatment with rifamycin?

Conclusions:

- Low strength of evidence from one poor quality randomized controlled trial (RCT) demonstrated that rifamycin is more effective compared to placebo in reducing the duration of TD caused by *E.Coli* (46 hours vs. 68 hours; p=0.0008).[1] In addition, low strength of evidence shows that a larger percentage of rifamycin-treated patients (81.4%) achieved clinical cure compared with placebo-treated patients (56.9%; difference=24.5%; p=0.0001; 95% Confidence Interval (CI) 11.3 to 37.7; Number Needed to Treat (NNT) 5).[1] Clinical cure was defined by the investigators as two or fewer soft stools and minimal enteric symptoms at the beginning of a 24-hour period or no unformed stools at the beginning of a 48-hour period.[1]
- A non-inferiority study at high risk of bias provides insufficient evidence that rifamycin was non-inferior to ciprofloxacin in treating non-dysenteric TD.[2] In this trial investigators reported the median time to last unformed stool (TLUS) in Per Protocol (PP) analysis of the rifamycin-treated group was 42.8 hours versus 36.8 hours in the ciprofloxacin group (p=0.0035 for non-inferiority).[2] There was no statistically significant difference in clinical cure rates between rifamycin (85%) compared to ciprofloxacin (84.8%; p=0.942).[2]
- There is low-quality evidence that the tolerability of rifamycin is comparable to placebo or ciprofloxacin. In the 2 low quality studies, constipation (3.5% rifamycin, 1.5% placebo) and headache (3.3% rifamycin, 1.9% ciprofloxacin) were the only reported treatment-emergent adverse events (TEAEs) that occurred with rifamycin at a rate greater than placebo or ciprofloxacin.[3] No severe adverse effects were reported during either RCT. Only 1% (n=6) of patients from both trials were reported to have discontinued the trials due to an adverse effect.[1,2]
- The safety of rifamycin has not been evaluated in pediatric patients, pregnant women, breast feeding women, or adults aged 65 years and older.
- The efficacy of rifamycin has not been demonstrated in infectious diarrhea or in TD due to pathogens other than *E.coli* or TD complicated by fever and bloody diarrhea. The safety of rifamycin has not been evaluated in pediatric patients.
- Evidence is insufficient to determine the comparative safety of rifamycin and rifaximin or azithromycin.

Author: Deanna Moretz, PharmD, BCPS

Recommendations:

- Designate rifamycin as non-preferred on the preferred drug list (PDL).
- Add rifamycin to PA criteria for rifaximin to ensure appropriate utilization of both medications. (**Appendix 2**).

Summary of Prior Reviews and Current Policy

Previous P and T Committee recommendations for drugs used to manage infectious diarrhea were addressed at the May 2015 meeting when PA criteria for the use of rifaximin in hepatic encephalopathy (HE) were presented. Use of rifaximin is restricted to Oregon Health Plan (OHP)-funded conditions such as prevention or treatment of HE. Rifaximin also has an FDA-approved indication for treatment of traveler's diarrhea caused by noninvasive strains of Escherichia coli. Both HE and infectious diarrhea are funded conditions under the OHP.

Background:

Travelers' diarrhea is defined as passage of 3 or more unformed stools plus at least 1 accompanying symptom in a 24 hour period that develops during or within 14 days of returning from travel to a resource-limited location.[4] Travelers' diarrhea is the most common illness afflicting travelers, and several observational studies report an incidence of 10-40% after a 2-week travel period depending on destination and traveler characteristics.[5] As a large number of individuals experiencing symptoms self-treat, the actual magnitude of the disease burden is uncertain.[3] Travel destination has a major impact on the risk for TD. According to the Centers for Disease Control and Prevention (CDC), the world is divided into 3 grades of TD risk: low, intermediate and high.[4]

- Low-risk countries include the United States, Canada, Australia, New Zealand, Japan, and countries in Northern and Western Europe.[4]
- Intermediate-risk countries include those in Eastern Europe, South Africa, and some Caribbean islands.[4]
- High-risk areas include most of Asia, the Middle East, Africa, Mexico, and Central and South America.[4]

Travelers' diarrhea is usually infectious and is caused by microbial pathogens endemic at the travel destination.[6] Most TD cases are contracted from contaminated food and less commonly from water.[1] Bacteria account for up to 90% of identified infectious etiologies for acute TD, predominately enterotoxigenic *E. coli* (ETEC), and enteroaggregative *E. coli* (EAEC), although there is regional variability.[7] Other bacterial pathogens that can cause TD include *Campylobacter jejuni*, *Shigella* species, and *Salmonella* species.[8] There is increasing recognition of *Aeromonas* species, *Plesiomonas* species, and newly identified pathogens (*Acrobacter, Larobacter*, enterotoxigenic *Bacteroides fragilis*) as potential causes of TD as well.[4] Regardless of cause, most cases of TD have a similar clinical appearance, with patients complaining of watery diarrhea with abdominal pain or cramps of variable severity.[8] The disease is present if travelers develop at their destination 3 or more unformed stools per 24 hours plus at least 1 additional symptom, such as abdominal cramps, tenesmus, nausea, vomiting, fever, or fecal urgency.[5] Travelers are recognized as an important vector for transmission of emerging and multi-drug resistant (MDR) enteropathogens globally.[9]

Rates of TD can be reduced if travelers are educated how to select safe food and beverages items.[8] Safe foods include those served steaming hot (≥ 59°C), dry items such as bread, and fruit that can be peeled.[8] Travelers should remember to use only beverages that are sealed, treated with chlorine, boiled, or are otherwise known to be purified.[4] When otherwise healthy travelers develop diarrhea they should be encouraged to consume fluids and salty foods.[8] Bismuth subsalicylate has antibacterial properties and prevents 65% of expected TD cases when taken at recommended doses (2.1 gm per day divided into 4 doses).[8] Probiotics are not recommended due insufficient evidence demonstrating their efficacy.[4] Antimotility agents provide symptomatic relief and are useful therapy in TD.[4] Loperamide or diphenoxylate can reduce frequency of bowel movements and therefore enable travelers to ride on public transportation.[4] Antimotility agents alone are not recommended for patients with bloody diarrhea or those who have diarrhea and fever.[4] Loperamide can be used in children, and liquid formulations are available.[4]

Antimicrobial therapy is not routinely recommended for mild TD, but should be considered for people with suspected *Shigella* or *Campylobacter* species and certain *E. coli* infections and moderate to severe TD symptoms.[8] Knowledge of global resistance patterns can help inform the choice of empiric antibiotics in returning travelers.[10] Increasing microbial resistance to the fluoroquinolones, especially among *Campylobacter* isolates, may limit their usefulness in many destinations, particularly South and Southeast Asia, where both *Campylobacter* infection and fluoroquinolone resistance is prevalent.[4] Increasing fluoroquinolone resistance has been reported from other destinations and in other bacterial pathogens, including in *Shigella* and *Salmonella*.[4] In general, azithromycin or a fluoroquinolone are recommended.[5] In particular, azithromycin is the preferred option for patients with fever or dysentery (bloody or mucoid diarrhea), pregnant women, children, and for travelers to locations (such as Southeast Asia) where fluoroquinolone-resistant pathogens are prevalent.[5] Fluoroquinolones had long been the first choice for treatment of travelers' diarrhea, but the emergence of resistance to this drug class and increased awareness of adverse events make the risk-benefit assessment less clear.[5] Rifaximin is an alternative for travelers' diarrhea suspected to be caused by noninvasive strains of *E. coli*, but its effectiveness against invasive pathogens is unknown, and it should not be used in patients with fever or bloody diarrhea.[5] Due to widespread resistance, sulfamethoxazole/trimethoprim is no longer recommended to treat TD.[3] A 2000 Cochrane review concluded that antibiotics shorten the overall duration of moderate to severe traveler's diarrhea to about a day and a half.[11] The mean duration of travelers' diarrhea, even if untreated, is 4 to 5 days.[12]

Guidelines:

American College of Gastroenterology

In 2016, the American College of Gastroenterology (ACG) published a clinical guideline focused on diagnosis, treatment, and prevention of acute diarrheal infections in adults.[13] No financial support was received by any of the authors for development of the recommendations. Potential conflicts of interest due to research support or participation on advisory boards was clearly stated in the publication. All 3 primary authors serve on the advisory boards of several pharmaceutical manufacturers including the manufacturer of rifaximin. One of the authors is an employee of the U.S. government and completed this work as part of his official duties. The evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.[14] Treatment recommendations based on moderate to high quality evidence are highlighted below. **Table 1** includes a summary of antibiotics recommended by the ACG to treat acute diarrhea symptoms in adults.

- The evidence does not support empiric anti-microbial therapy for routine acute diarrheal infection, except in cases of TD where the likelihood of bacterial pathogens is high enough to justify the potential side effects of antibiotics (Strong recommendation, high level of evidence).[13]
- Bismuth subsalicylates can be administered to control rates of passage of stool and may help travelers function better during bouts of mild to moderate illness (Strong recommendation, high level of evidence).[13]
- In patients receiving antibiotics for TD, adjunctive loperamide therapy can be administered to decrease duration of diarrhea and increase chance for a cure (Strong recommendation, moderate level of evidence).[13]

Table 1. Acute diarrhea treatment recommendations for adults[13]

Antibiotic	Dose	Treatment Duration
Levofloxacin	500 mg orally	Single dose - If symptoms not resolved after 24 hours, complete a 3 day course
Ciprofloxacin	750 mg orally **OR** 500 mg orally once a day	Single dose - If symptoms not resolved after 24 hours, complete a 3 day course 3-day course
Ofloxacin	400 mg orally	Single dose - If symptoms not resolved after 24 hours, complete a 3 day course
Azithromycin[a,b]	1000 mg orally **OR**	Single dose - If symptoms not resolved after 24 hours, complete a 3 day course

	500 mg once a day	3-day course[b]
Rifaximin[c]	200 mg orally three times a day	3-days (in patients > 12 years old)

a. Use empirically as first-line in Southeast Asia and India to cover fluoroquinolone resistant *Campylobacter* or in other geographic areas if *Campylobacter* or resistant ETEC are suspected.
b. Preferred regimen for dysentery or febrile diarrhea.
c. Do not use if clinical suspicion for *Campylobacter, Salmonella, Shigella*, or other causes of invasive diarrhea.

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

Clinical Efficacy:

Rifamycin, an antibiotic closely related to rifaximin, binds to bacterial DNA-dependent RNA polymerase, blocking one of the steps in DNA transcription.[15] This results in inhibition of bacterial synthesis and growth. The FDA approved indication for rifamycin is treatment of TD caused by non-invasive species of *E.Coli* in adults.[15] Rifamycin is poorly absorbed into the systemic circulation after oral administration.[15] It is manufactured with an enteric coating which allows the delivery of the active ingredient to the distal small bowel and colon.[15] Administration of rifamycin directly to the colonic lumen minimizes activity on the beneficial flora of the upper intestinal tract.[15] The Food and Drug Administration (FDA) approval of rifamycin was based on data from two randomized, multi-center, controlled Phase 3 clinical trials which were conducted entirely outside of American research sites. Trial 1 (NCT01142089), a placebo-controlled superiority study, was conducted at sites in Guatemala and Mexico. This trial was the primary basis for assessment of efficacy by the FDA.[3] The data from Trial 2 (NCT01208922), a non-inferiority comparison of rifamycin to ciprofloxacin, was considered supportive for efficacy in the FDA review.[3] Trial 2 was conducted at clinical sites in India, Guatemala and Ecuador.[2] This trial was funded by a different manufacturer than Trial 1 and was not conducted under an American Investigational New Drug (IND) application.[3]

Trial 1 enrolled 264 adults traveling to Mexico or Guatemala experiencing acute diarrhea.[1] Subjects were randomized 3:1 to rifamycin (400 mg orally twice daily for 3 days) or placebo. Patients with fever and/or bloody stools were excluded from the trial. Patients recorded in diaries the date, time, and consistency of stools (formed, soft, or watery), study drug administration, symptoms of enteric infection, and adverse events.[1] Safety and efficacy were assessed at visit 2 (day 2), visit 3 (day 4 or 5), and visit 4 (days 6–10).[1] Drug compliance was verified by review of diaries and by counting remaining tablets when medicine containers were returned.[1] Stool samples were collected at visit 1 and visit 3 and sent to a central laboratory (Center for Infectious Diseases at University of Texas School of Public Health) for pathogen identification and antibiotic susceptibility testing.[1] Patients were eligible to receive rescue therapy if diarrhea and/or symptoms of enteric infection worsened or failed to improve. Patients receiving rescue therapy were withdrawn from the study and given the maximum TLUS (time to last unformed stool) value of 120 hours.[1] The most common reason for not completing the trial was that the patient required rescue medication, seen in 12.3% of placebo patients and 8.5% of rifamycin patients.[1]

The primary endpoint was the length of time between administration of the first medication dose to last unformed (watery or soft) stool (TLUS) before achieving clinical cure.[1] Clinical cure was defined as two or fewer soft stools and minimal enteric symptoms at the beginning of a 24-hour period or no unformed stools at the beginning of a 48-hour period.[1] The investigators reported TLUS was significantly shorter in the rifamycin group (median: 46.0 hours) compared with placebo (median: 68.0 hours; p=0.0008, due to the distribution of placebo TLUS values, it was not possible to compute a 95% confidence interval for this difference).[1] In addition, a larger percentage of rifamycin-treated patients (81.4%) achieved clinical cure compared with placebo-treated patients (56.9%) [Difference=24.5%; p=0.0001; 95% CI 11.3 to 37.7; NNT 5].[1] The predominant pathogen identified from collected stool samples was *E. coli*.[1]

Trial 2 was a randomized, double-blind, multi-center, non-inferiority trial in which subjects were randomized 1:1 to a 3-day course of rifamycin (400 mg orally twice daily) or ciprofloxacin (500 mg orally twice daily).[2] A total of 835 subjects traveling to India, Guatemala, or Ecuador were enrolled in the trial. Most of the study centers (89%) were located in India.[2] Inclusion and exclusion criteria were similar to Trial 1, although Trial 2 excluded subjects traveling from the United States, Canada and Australia for reasons that were not clearly stated in the FDA summary report.[3] Most to the travelers in Trial 2 originated in Europe.[3] Safety and efficacy were evaluated at Visit 2 (day 2), Visit 3 (day 4 or 5), and the final visit (day 6). Stool samples were collected at the baseline visit and the end of treatment visit and sent to a central laboratory for pathogen identification and antibiotic susceptibility testing. If a patient received rescue therapy within 120 hours after ingestion of the first dose of the study drug, the patient was considered a treatment failure.[2]

The primary endpoint for Trial 2 was TLUS as documented by subjects in a daily diary over 5 days, which was similar to Trial 1.[2] The median TLUS for ciprofloxacin-treated patients was assumed as 27.5 hours and 28.5 hours for rifamycin.[2] The non-inferiority margin was defined by a maximally acceptable difference in the median TLUS of 8.5 hours (with a corresponding delta = 0.764 for the hazard ratio) between rifamycin and ciprofloxacin.[2] The confirmatory non-inferiority test was performed on the per-protocol (PP) analysis set and confirmed with a sensitivity test of the intention-to-treat (ITT) population.[2] Patients with lack of compliance, intake of forbidden concomitant medication, violation of eligibility criteria or early discontinuation due to adverse effects without causal relationship with study drug, were excluded from the PP population.[2] In total, 835 patients were randomized and received at least one dose of study medication.[2] The PP population consisted of 767 subjects (8.1% attrition).[2]

The median TLUS in the PP analysis of the rifamycin-treated group was 42.8 hours versus 36.8 hours in the ciprofloxacin group (p=0.0035), indicating non-inferiority of rifamycin to ciprofloxacin.[2] In the ITT analysis, median TLUS in the rifamycin-treated group was 44.3 hours versus 40.3 hours in the ciprofloxacin-treated group (p=0.0011 for non-inferiority).[2] Clinical cure was defined as 24 hours with no clinical symptoms and no more than 2 soft stools or 48 hours without symptoms or any unformed stools.[2] There was no statistically significant difference in clinical cure rates between rifamycin (85%) compared to ciprofloxacin (84.8%; p=0.942).[2] In addition, the percentage of patients requiring rescue therapy was similar in both groups (rifamycin 2.6% vs. ciprofloxacin 1%; p =0.072).[2] The most common pathogen identified from collected stool samples was *E. coli*, although in 37.1% of patients no pathogen could be isolated.[2] Additional information about Trial 1 and Trial 2 is summarized in **Table 3.**

Trial Limitations:

According to the FDA summary, data for both Phase 3 trials of rifamycin were of adequate quality.[3] For Trial 1, the investigators' analysis of the primacy efficacy endpoint was accurate, but the analyses for a number of secondary endpoints (e.g. treatment failure, microbiological cure points) were inaccurate.[3] The FDA reviewer noted that the "time to unformed stool" is a misnomer.[3] For example, if a participant had a watery stool at 12 hours, soft stools at 30 and 35 hours, with no additional unformed stools, fever, or enteric symptoms, then the participant achieved clinical cure prior to the unformed stools at 30 and 35 hours.[3] Therefore, the TLUS value is 12 hours, even though there were two subsequent unformed stools.[3] In addition, the FDA reviewer noted the definition of clinical cure seems inadequate, as it accounts for rescue medication administered by study physicians but ignores prohibited medications self-administered (e.g., loperamide) or prescribed or administered by non-study physicians (e.g., antibacterial drugs).[3] Since use of such prohibited medications prior to the achievement of clinical cure (as defined by the investigators) could have contributed to that achievement, ignoring the use of prohibited medications when assessing clinical cure confounds the attribution of cure to the study medication.[3] The FDA reviewer noted in Trial 1 that 2% of patients (n=4) took prohibited medications and 5% of subjects (n=10) took an additional 2 doses of medication (or 1 extra treatment day) in the rifamycin-treated arm of the ITT population.[3] The extra doses were supplied as a contingency reserve in case of loss or mishap. However, one primary investigator prescribed additional doses to 4 subjects due to continued symptoms. It is not clear why the other subjects took the extra doses.[3] In Trial 2, 2% of patients in both arms (rifamycin and ciprofloxacin) took prohibited

medications in the PP population set.[3] Nineteen subjects (4.5%) in the rifamycin arm and 13 subjects (3.1%) in the ciprofloxacin did not submit complete diary cards.[3]

An additional concern was the incorrect handling of missing TLUS observations due to incomplete diary recordings. For example, one subject in the rifamycin arm maintained the daily diary for only 24 hours and recorded no stools during that period, the investigator assigned that subject a censored TLUS of 24 hours, meaning that the true (but unobserved) TLUS value is larger than 24 hours.[3] However, it is possible that the participant's true TLUS value is 0.[3] This would be the case if the participant also had no unformed stools during hours 24-48, as then hours 0-48 would constitute a 48-hour qualifying period for clinical cure and clinical cure would be achieved at hour 0.[3] Hence, this participant's TLUS value should be censored at 0 hours rather than 24 hours.[3] Instances of censoring due to incomplete diaries could be cases of informative censoring.[3] Four subjects submitted incomplete symptom diaries in Trial 1.

Since the non-inferiority design of Trial 2 did not include a placebo arm, the investigators had to rely on the use of historical information to determine efficacy, which means the results should be interpreted with caution.[3] The FDA reviewers also noted the establishment of the non-inferiority margin using the hazard ratio was flawed.[3] In order to determine a hazard ratio corresponding to a median TLUS margin of 8.5 hours, the investigators made strong assumptions about the true value of the ciprofloxacin median TLUS value and about the distribution of the rifamycin and ciprofloxacin TLUS values.[3] It is highly implausible that a hazard ratio of 0.764 corresponds to a median margin of 8.5 hours, given the true but unknown ciprofloxacin median TLUS and the true but a priori unknown distributions of the rifamycin and ciprofloxacin TLUS values.[3] The specification of a hazard ratio does not accurately specify a non-inferiority margin.[3]

In summary, Trial 1 provides moderate quality evidence of the effectiveness of rifamycin in treating TD caused by non-invasive E.coli in adults who were not experiencing fever or bloody stools compared to placebo.[1] Trial 2 provides low quality evidence that rifamycin is non-inferior to ciprofloxacin in treating non-dysenteric TD.[2] Rifamycin has a similar spectrum of activity as rifaximin. Both antibiotics have low systemic absorption and duration of therapy (3-day course of treatment). Similar to rifaximin, rifamycin shortens the course of TD by approximately 1 day.[3] The efficacy of rifamycin has not been demonstrated in infectious diarrhea or in TD due to pathogens other than E.coli or complicated by fever and bloody diarrhea. The efficacy or safety of rifamycin has not been evaluated in pediatric patients.

Clinical Safety:
In phase 3 studies, headache and constipation were the only reported treatment-emergent adverse events (TEAEs) that occurred with rifamycin at a rate greater or equal to 2% and higher than placebo or ciprofloxacin.[3] Discontinuation of rifamycin due to adverse reactions occurred in 1% of patients during the 2 clinical trials (n=619 total enrollment).[16] The most frequent adverse reactions leading to discontinuation of rifamycin were abdominal pain (0.5%) and pyrexia (0.3%).[15] In Trial 1 (placebo-controlled), the adverse reaction that occurred in at least 2% of rifamycin-treated patients (n=199) and with an incidence higher than in the placebo group was constipation (3.5% rifamycin, 1.5% placebo).[15] In Trial 2 (active comparator: ciprofloxacin), the adverse reaction that occurred in at least 2% of rifamycin-treated patients (n=420) and with an incidence higher than in the ciprofloxacin group was headache (3.3% rifamycin, 1.9% ciprofloxacin).[15] No deaths occurred in either clinical trial.

Look-alike / Sound-alike Error Risk Potential: Rifaximin

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Reduction in symptoms (diarrhea, abdominal pain, nausea)
2) Resolution of symptoms (clinical cure)
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Time to last unformed stool (TLUS)
2) Percentage of patients with a clinical cure (two or fewer soft stools and minimal enteric symptoms at the beginning of a 24-hour period or no unformed stools at the beginning of a 48-hour period)

Table 2. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Binds to bacterial DNA-dependent RNA polymerase, blocking one of the steps in DNA transcription. This results in inhibition of bacterial synthesis and growth of bacteria.
Oral Bioavailability	Minimal systemic absorption: less than 0.1% oral bioavailability
Distribution and Protein Binding	Protein Binding: 80%
Elimination	Fecal: 86%
Half-Life	Unknown
Metabolism	Not applicable

Table 3. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/N NT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Dupont, et al.[1] Phase 3 RCT, DB, MC, PC N=264	1. Rifamycin 400 mg orally twice daily for 3 days 2. Placebo orally twice daily for 3 days	Demographics: 1. Median age: 24 yo 2. 50% female 3. Duration of diarrhea: 33 hrs. 4. Country visited: Mexico - 66% Guatemala - 34% Key Inclusion Criteria: 1. ≥ 18 years of age 2. Travel from industrialized country within 30 days before randomization 3. ≥ 3 unformed stools within 24 hrs. 4. Duration of illness < 72 hrs. 5. At least one symptom of enteric infection (nausea, vomiting, abdominal pain, defecation urgency) Key Exclusion Criteria: 1. Fever > 38°C 2. Symptom of systemic infection 3. Infection with non-bacterial pathogen 4. Grossly bloody stool 5. Severe dehydration 6. Taking more than 2 doses of AD medicine within 24 hrs. 7. Taking an antibiotic against gram negative bacteria within 7 days	ITT: (all subjects who received 1 dose of medication) 1. 199 2. 65 PP: (all subjects that completed the trial) 1. 179 2. 53 Attrition: 1. 21 (10.6%) 2. 12 (18.5%)	Primary Endpoint: Length of time to TLUS 1. 46 hrs. 2. 68 hrs. Difference = 22 hours; p=0.0008 95% CI not able to be calculated Secondary Endpoint: Clinical Cure (≤2 stools/24 hrs. or 0 stools/48 hrs.) 1. 163 (81.4%) 2. 37 (56.9%) Difference = 24.5% p=0.0001 95% CI 11.3 to 37.7	NA 24.5%/ 5	Study withdrawal due to AE 1. 1 (0.5%) 2. 9 (13.5%) Diarrhea 1. 20 (10%) 2. 11 (16.9%) Headache 1. 17 (8.5%) 2. 6 (9.2%) Constipation 1. 7 (3.5%) 2. 1 (1.5%) p value and 95% CI NR for all	NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 3:1 via blocks of 4 developed by an independent statistician. Stratified by site. Baseline characteristics similar in both arms. Performance Bias: Unclear. Protocol deviations varied from site to site as reported in FDA summary. Blinding was not clearly described. Detection Bias: Unclear. Investigators and patients blinded to study medication via the blister packet in which medication was dispensed. Patients reported symptoms in a daily diary and interpretation of results may be subject to bias. Attrition Bias: Low. Higher withdrawal in placebo group due to the need for rescue therapy which may lead to a more conservative estimate of effect. Reporting Bias: Unclear. Protocol unavailable. Other Bias: Unclear. Trial funded by Santarus. Several investigators received consulting fees from Santarus or were employed by Santarus. **Applicability**: Patient: Primarily applies to travelers in Mexico and Central America. Patients with fever or bloody diarrhea were excluded. Intervention: Appropriate dosing based on Phase 2 trials of rifamycin. Comparator: Compared to placebo to demonstrate superiority. Active comparator could have been rifaximin or azithromycin to provide comparative safety/efficacy data to standard of care. Outcomes: TLUS reported by patients in a daily diary, subject to misinterpretation by investigators. Definition of clinical cure was ambiguous. Setting: 8 centers in Mexico (n=175) and 2 in Guatemala (n=89).

2. Steffen, et al.[2] Phase 3 RCT, DB, MC N=835	1.Rifamycin 400 mg orally twice daily for 3 days 2.Ciprofloxacin 500 mg orally twice daily for 3 days	Demographics: 1. Median age: 35 yo 2. 50% female 3. Country visited: India - 96% Guatemala - 2% Ecuador – 2% Key Inclusion Criteria: 1. ≥ 18 years of age 2. Travel from industrialized country within 30 days before randomization 3. ≥ 3 unformed stools within 24 hrs. 4. Duration of illness < 72 hrs. 5. At least one symptom of enteric infection (nausea, vomiting, abdominal pain, defecation urgency) Key Exclusion Criteria: 1. Fever > 38°C 2. Symptom of systemic infection 3. Infection with non-bacterial pathogen 4. Grossly bloody stool 5. Severe dehydration 6. Taking more than 2 doses of AD medicine within 24 hrs. 7. Resident of any country with high incidence rates of diarrhea 8. Travelers from the US, Canada, and Australia	ITT: (all subjects who received 1 dose of medication) 1. 420 2. 415 PP: (all subjects who completed at least 2 days of diary recordings) 1. 384 2. 383 Attrition: 1. 36 (8.5%) 2. 42 (10%)	Primary Endpoint: Noninferiority assessment of median length of time to TLUS in PP population 1. 42.8 hrs. 2. 36.8 hrs. p=0.0035 for noninferiority HR = 0.943 95% CI 0.804 to 1.100 Noninferiority assessment of median length of time to TLUS in ITT population 1. 44.3 hrs. 2. 40.3 hrs. P=0.0011 for noninferiority HR = 0.962 95% CI = 0.826 to 1.119 Secondary Endpoint: Clinical Cure (≤2 stools/24 hrs. or 0 stools/48 hrs.) 1. 357 (85.0%) 2. 352 (84.8%) Difference = 0.2% p=0.942 Requirement of Rescue Therapy 1. 11 (2.6%) 2. 4 (1%) Difference = 1.6% p=0.072	NA NA NS NS	Incidence of AEs 1. 62(14.8%) 2. 62 (14.9%) Incidence of ADRs 1. 34 (8.1%) 2. 31 (7.5%) Study withdrawal due to AE 1. 1 (<1%) 2. 0 p value and 95% CI NR for all	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear. Randomized 1:1 via blocks of 4 using a computer-generated list of numbers. Baseline characteristics similar in both arms. Performance Bias: Unclear. Protocol deviations varied from site to site as reported in FDA summary. Investigators dispensed blinded study medication according to randomization schedule. Detection Bias: Unclear. Investigators and patients blinded to study medication via the package medication was dispensed in. Patients reported symptoms in a daily diary and interpretation of results may be subject to bias. Attrition Bias: Low. 3% of patient withdrew due to lack of efficacy, or follow-up. 7-8% withdrew due to protocol deviations. Reporting Bias: Unclear. Protocol unavailable. Other Bias: Unclear. Trial funded by Dr. Falk Pharma GmBH. Several investigators received honoraria from Dr. Falk Pharma GmBH or were employed by Dr. Falk Pharma GmBH. **Applicability**: Patient: Primarily applies to travelers to India. Patients with fever or bloody diarrhea were excluded. Excluded U.S. travelers, which limits generalizability to U.S. subjects. Patients in this trial were on average 10 years older than Trial 1. Intervention: Appropriate dosing based on Phase 2 trials of rifamycin. Comparator: Compared to ciprofloxacin to establish non-inferiority. No placebo armed included to assess efficacy of rifamycin. Active comparator could have been rifaximin to provide comparative safety/efficacy data with a similar antibiotic. Outcomes: TLUS reported by patients in a daily diary, subject to misinterpretation by investigators. Definition of clinical cure was ambiguous. Setting: 17 centers in India (n=805), 1 in Guatemala (n=15) and 1 in Ecuador (n=15).

Abbreviations : AD = antidiarrheal; ADR = adverse drug event; AE = adverse effect; ARR = absolute risk reduction; CI = confidence interval; DB = double-blinded; Hrs. = hours; ITT = intention to treat; MC = multi-center; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; PC = placebo-controlled; PP = per protocol; RCT = randomized controlled trial; TLUS = time to last unformed stool; US = United States; YO = years old

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Appendix 1: Prescribing Information Highlights

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

AEMCOLO (rifamycin) delayed-release tablets, for oral use.
Initial U.S. Approval: 2018

----------INDICATIONS AND USAGE----------
AEMCOLO is a rifamycin antibacterial indicated for the treatment of travelers' diarrhea caused by noninvasive strains of *Escherichia coli* in adults. (1.1)

Limitations of Use:
AEMCOLO is not recommended for use in patients with diarrhea complicated by fever and/or bloody stool or due to pathogens other than noninvasive strains of *E. coli*. (1, 5.1, 14)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of AEMCOLO and other antibacterial drugs, AEMCOLO should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria (1.2).

----------DOSAGE AND ADMINISTRATION----------
- The recommended dosage of AEMCOLO is 388 mg (two tablets) orally twice daily for three days. (2.1)
- Take each dose with a glass of liquid. Do **NOT** take AEMCOLO concomitantly with alcohol. (2.1)
- AEMCOLO can be taken with or without food. (2.1)
- Swallow AEMCOLO tablets whole. Do NOT crush, break or chew the tablets. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Delayed-Release Tablets: 194 mg rifamycin. (3)

----------CONTRAINDICATIONS----------
AEMCOLO is contraindicated in patients with a known hypersensitivity to rifamycin, any of the other rifamycin class antimicrobial agents (e.g. rifaximin), or any of the components in AEMCOLO (4)

----------WARNINGS AND PRECAUTIONS----------
- Risk of Persistent or Worsening Diarrhea Complicated by Fever and/or Bloody Stool: AEMCOLO was not shown to be effective in patients with diarrhea complicated by fever and/or bloody stool or diarrhea due to pathogens other than noninvasive strains of *E. coli* and is not recommended for use in such patients. Discontinue use if diarrhea gets worse or persists more than 48 hours, and consider alternative antibacterial therapy. (1. 5.1)
- *Clostridium difficile*-associated Diarrhea: Evaluate if diarrhea occurs after therapy or does not improve or worsens during therapy. (5.2)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > 2%) are headache and constipation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Aries Pharmaceuticals Inc. at 888-ARIES-08 (888-274-3708) option 1 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised:11/2018

Appendix 2: Proposed Prior Authorization Criteria

Rifaximin (Xifaxan®) and Rifamycin (Aemcolo®)

Goal(s):

- Promote use that is consistent with medical evidence and product labeling.

Length of Authorization:

- 3 days for traveler's diarrhea caused by non-invasive strains of *E.Coli* for rifaximin or rifamycin.
- Up to 12 months for hepatic encephalopathy for rifaximin.

Requires PA:

- Rifaximin and Rifamycin

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication and is the indication funded by OHP?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis traveler's diarrhea caused by non-invasive strains of E.Coli?	**Yes:** Go to #4	**No:** Go to # 5

Approval Criteria		
4. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee. • Preferred products for traveler's diarrhea are dependent on traveler's destination and resistance patterns in that area. Refer to **Table 1** for adult treatment recommendations.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Approve for 3 days.
5. Is the request for rifaximin to prevent or treat hepatic encephalopathy?	**Yes**: Go to #6	**No**: Pass to RPh. Deny; not funded by OHP or for medical appropriateness
6. Is the patient currently managed with a regularly scheduled daily regimen of lactulose?	**Yes**: Go to #8	**No**: Go to #7
7. Does the patient have a contraindication to lactulose?	**Yes**: Go to #8	**No**: Pass to RPh Deny; medical appropriateness Note: studies demonstrate effectiveness of rifaximin as add-on therapy to lactulose.
8. Is the patient currently prescribed a benzodiazepine drug?	**Yes**: Go to #9	**No**: Approve for up to 12 months

Approval Criteria		
9. Is the patient tapering off the benzodiazepine? Note: tapering process may be several months	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness Note: studies explicitly excluded use of benzodiazepines and benzodiazepine-like drugs because of their risk for precipitating an episode of hepatic encephalopathy**.**

Table 1. Acute diarrhea treatment recommendations for adults[1]

Antibiotic	Dose	Treatment Duration
Levofloxacin	500 mg orally	Single dose - If symptoms not resolved after 24 hours, complete a 3 day course
Ciprofloxacin	750 mg orally **OR** 500 mg orally once a day	Single dose - If symptoms not resolved after 24 hours, complete a 3 day course 3-day course
Ofloxacin	400 mg orally	Single dose - If symptoms not resolved after 24 hours, complete a 3 day course
Azithromycin[a,b]	1000 mg orally **OR** 500 mg once a day	Single dose - If symptoms not resolved after 24 hours, complete a 3 day course 3-day course[b]
Rifaximin[c]	200 mg orally three times a day	3-days (in patients > 12 years old)

a. Use empirically as first-line in Southeast Asia and India to cover fluoroquinolone resistant *Campylobacter* or in other geographic areas if *Campylobacter* or resistant enterotoxigenic *E. coli* are suspected.

b. Preferred regimen for dysentery or febrile diarrhea.

c. Do not use if clinical suspicion for *Campylobacter, Salmonella, Shigella*, or other causes of invasive diarrhea.

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