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, November 21st, 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)
1:25 PM	II. CONSENT AGENDA TOPICS	T. Klein (Chair)

A. State Annual Report
B. Quarterly Utilization Reports
C. Antifungals (oral and topical) Class Update
D. Anticoagulants Class Update
   1. Public Comment

III. DUR ACTIVITIES

1:30 PM	A. ProDUR Report	R. Holsapple (DXC)
	B. RetroDUR Report	D. Engen (OSU)
	C. Oregon State Drug Review	K. Sentena (OSU)

1. Oregon Health Authority Mental Health Clinical Advisory Group (MHCAG) Recommendations for Treatment of Schizophrenia
2. Stimulant Use in Excessive Somnolence Disorders

V. DUR NEW BUSINESS

1:45 PM	A. Substance Use Disorders, Opioid and Alcohol 1. Literature scan 2. Policy Proposal/Prior Authorization Criteria 3. Public Comment 4. Discussion of Clinical Recommendations to OHA	D. Moretz (OSU) S. Servid (OSU)
2:05 PM	B. Antidepressant Use in Children 1. Drug Use Evaluation/Safety Edit 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	S. Servid (OSU)
2:25 PM	C. Dupixent® (dupilumab) Prior Authorization Update 1. Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	D. Moretz (OSU)

VI. PREFERRED DRUG LIST NEW BUSINESS

2:35 PM	A. Aemcolo™ (rifamycin) New Drug Evaluation 1. New Drug Evaluation/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	S. Servid (OSU)
2:50 PM	B. Arikayce® (amikacin) New Drug Evaluation 1. New Drug Evaluation/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	D. Engen (OSU)
3:05 PM	BREAK	
3:15 PM	C. Drugs for Gaucher Disease Class Review 1. Class Review/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	S. Servid (OSU)
3:30 PM	D. Ruzurgi® and Firdapse® (amifampridine) New Drug Evaluations 1. New Drug Evaluations/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	D. Engen (OSU)
3:45 PM	E. Cholbam® (cholic acid) New Drug Evaluation	D. Moretz (OSU)

1. New Drug Evaluation/Prior Authorization Criteria
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

4:00 PM VII. EXECUTIVE SESSION

4:50 PM VIII. RECONVENE for PUBLIC RECOMMENDATIONS

IX. ADJOURN

4:55 PM X. OHA RULES ADVISORY COMMITTEE J. Torkelson (OHA)

1. Public Comment

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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, September 26, 2019 1:00 - 5:00 PM

DXC Conference Room

4070 27th Ct. SE

Salem, OR 97302

MEETING AGENDA

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; Bill Origer, MD; Cathy Zehrug RPh; James Slater PharmD; Mark Helm MD, MBA, FAAP; Russell Huffman, DNP, PMHNP; Stacy Ramirez, PharmD,

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

Staff Present: Roger Citron, RPh; David Engen, PharmD; Richard Holsapple, RPh; Megan Herink, PharmD; Deanna Moretz, PharmD; Sarah Servid, PharmD; Deborah Weston; Trevor Douglass, DC, MPH; Brandon Wells; Jennifer Torkelson; Jennifer Bowen;

Staff Present by Phone: Kathy Sentena, PharmD;

Audience: Russ Rahimtoola PTC Therapeutics; Tena Aadel PTC Therapeutics; Alexis Russell PTC Therapeutics*; Lydia Shenouda, Avexis, Inc.*; Keith Dilly, Avexis Inc.; Paul Bonham, Avexis Inc.; Bobbi Jo Drum, BMS; Lisa Borland, Sarepta*; Kevin Ho, Sanofi Genzyme*; Gregg Resnick, Vertex Pharmaceuticals; Laura Jeffcoat, AbbVie; Angela Walter, Sanofi Genzyme*; Joseph Triong, Vertex Pharmaceuticals*; Keri Smith, ViiV; Michelle Bice, Gilead Sciences; Lauren Nelson, Sanofi Genzyme*; Stuart O'Brochta , Gilead Sciences*; John O'Malley, Sanofi Genzyme; Brad Peacock, Gilead Sciences; Austin Landerville,; Zulema Lescas; Paul Williams, Genentech; Jesse McCoy, Genzyme; Bill McDougal, Biogen; Gloria Montesanto, Sanofi Genzyme; Kaysei Bam, Biogen; Deanne Calvert, Sanofi Genzyme*; Kathleen Mullane, Safeway; Camille Kerr, Amigen; Lisa Knutson, Sanofi Genzyme; Lauren Sandt, Caring Ambassadors; Lori McDermott, Supernus; Kim Bennett; Danielle Shannon, WVP Health Authority; Erika Finanger*; Desiree Allen, AbbVie; Jon Taylor , Alnylam; Diann Matthews, Merck; Chris Johnson, Spark; Geetika Gupta, Merck; Amy Yang*, OHSU;

(*) Provided verbal testimony

Written testimony provided: Posted to OSU Website

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I. CALL TO ORDER

A. The meeting was called to order at approximately 1:05 pm. Introductions were made by Committee members and staff.
B. Conflict of Interest Declaration - No new conflicts of interest were declared.
C. Approval of July 2019 minutes presented by Mr. Citron
ACTION: Motion to approve, 2nd , all in favor
D. Department Update: Trevor Douglas – Mental Health Clinical Advisory Group – Amanda Parrish appointed to coordinator

II. CONSENT AGENDA TOPICS

A. Oral Muscle Relaxants Literature Scan
B. Herpes Simplex Virus Literature Scan
C. Insulins Class Update
D. Antidepressants - Reviewed in July 2019
Recommendation:
- Make no changes to the PMPDP based on clinical evidence
- Evaluate comparative drug costs in executive session

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

III. PREFERRED DRUG LIST NEW BUSINESS

A. Drug Class Literature Scans
1. Hepatitis C, Direct-Acting Antivirals
Dr. Herink presented the proposal to:
- Approve updated prior authorization (PA) criteria
- Recommend maintenance of Table in the PA criteria to reflect ongoing updates to FDA-approved regimens for preferred regimens
- Make no changes to the PMPDP based on clinical evidence
- Evaluate comparative drug costs in executive session

ACTION: The Committee recommended moving the request for baseline RNA level to question #2 when asking about diagnosis (ie through positive detection of HCV viral load)
Motion to approve, 2nd, all in favor

2. Tobacco Smoking Cessation
Dr. Engen presented the proposal to:
- Update PA criteria to implement an age limit for varenicline
- Make no changes to the PMPDP based on clinical evidence
- Evaluate comparative drug costs in executive session

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

3. Drugs for Duchenne Muscular Dystrophy
Dr. Servid presented the proposal to:

- Update PA criteria to include updated FDA-approved ages and assessment of immunization status prior to initiation of treatment with deflazacort

ACTION: The Committee recommended modifying questions #7 to specify 2 MMR and 2 varicella vaccinations and #9 to clarify which mutations are amenable to exon 51 skipping
Motion to approve, 2nd, all in favor

B. Oral Cystic Fibrosis Modulators Prior Authorization Update
Dr. Herink presented the proposal to:

- Update PA criteria to reflect recent changes in FDA approved labels for ivacaftor and tezacaftor/ivacaftor
- Revise PA criteria to list FDA-approved indications and ages in a table which will facilitate more streamlined PA updates for expanded indications

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

C. Opioid Class Update
Dr. Herink presented the proposal to:

- Revise PA criteria as follows:
    - Add dihydrocodeine morphine milliequivalents to opioid conversion chart listed in SAO PA criteria
    - Add pain associated with sickle cell disease and severe burn injury as an exclusion to SAO and LAO PA criteria
    - Add concomitant benzodiazepine/CNS depressant use as an assessment to SAO and LAO PA criteria
    - Remove taper plan for patients using chronic SAO's for back and spine, based on HERC guidance
    - Retire codeine PA criteria and add a question about use of codeine and tramadol to the SAO PA criteria to insure appropriate use in patients under the age of 19 years based on FDA safety alerts
- Make no changes to the PMPDP based on clinical evidence
- Evaluate comparative drug costs in executive session

ACTION: The Committee recommended: modifying the question on the Prescription Drug Monitoring Program (PDMP) to verify that opioid prescribing is appropriate rather than from a single provider; add PEG score to the list of examples documenting improvement in question #17 in the SAO criteria; and to add a note recommending against pediatric use for tramadol in the dosing table
Motion to approve, 2nd, all in favor

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D. Vyndaqel® and Vyndamax® (tafamidis) New Drug Evaluation

Dr. Herink presented the proposal to:

- Designat Vyndaqel and Vyndamax as non-preferred medications in the Amyloidosis Agents class
- Modify PA criteria for Drugs for Transthyretin-Mediated Amyloidosis to ensure appropriate use of tafamidis

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

E. Spinal Muscular Atrophy Class Update and New Drug Evaluation

Dr. Moretz presented the proposal to:

- Implement PA criteria to ensure one time administration of onasemnogene abeparvovec in appropriate SMA pediatric populations per the FDA labeling
- Revise nusinersen PA criteria to include an assessment of onasemnogene abeparvovec administration prior to nusinersen initiation
- Evaluate comparative drug costs in executive session

ACTION: The Committee recommended adding language to the nusinersen renewal criteria regarding stabilization in a meaningful manner

Motion to approve, 2nd, all in favor

F. Bone Metabolism Drugs Class Update and New Drug Evaluation

Dr. Moretz presented the proposal to:

- Maintain romosozumab as a non-preferred agent on the PMPDP
- Update clinical prior authorization (PA) criteria for bone metabolism agents to include romosozumab
- Evaluate comparative drug costs in the executive session

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

G. Drugs for Fabry Disease Class Review

Dr. Moretz presented the proposal to:

- Designate agalsidase beta and migalastat as non-preferred agents on the PMPDP
- Implement PA criteria for the Fabry disease treatments to ensure use according to FDA-approved indications

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

H. Aemcolo™ (rifamycin) New Drug Evaluation

Topic Deferred to a Future Meeting

IV. EXECUTIVE SESSION

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Members Present by Phone: David Pass, MD; Kelley Burnett, DO; Kathy Sentena, PharmD; Caryn Mickelson, PharmD

Staff Present: Roger Citron, RPh; David Engen, PharmD, CGP; Richard Holsapple, RPh; Deanna Moretz, PharmD; Sarah Servid, PharmD; Trevor Douglass, DC, MPH; Brandon Wells; Jennifer Torkelson; Jennifer Bowen

V. RECONVENE for PUBLIC RECOMMENDATIONS

A. Oral Muscle Relaxants Literature Scan
Recommendation: make methocarbamol preferred on the PDL
ACTION: Motion to approve, 2nd, all in favor

B. Herpes Simplex Virus Literature Scan
Recommendation: make valacyclovir tablets preferred on the PDL
ACTION: Motion to approve, 2nd, all in favor

C. Insulins Class Update
Recommendation: make insulin glulisine (pens and vials); insulin regular, human U-500 pen; Humalog Mix 75/25 and 50/50 KwikPens; and insulin detemir vials preferred on the PDL
ACTION: Motion to approve, 2nd, all in favor

D. Antidepressants
Recommendation: make no changes to the PDL
ACTION: Motion to approve, 2nd, all in favor

E. Hepatitis C, Direct-Acting Antivirals
Recommendation: make Zepatier non-preferred on the PDL
ACTION: Motion to approve, 2nd, all in favor

F. Tobacco Smoking Cessation
Recommendation: make no changes to the PDL
ACTION: Motion to approve, 2nd, all in favor

G. Opioid Class Update
Recommendation: make no changes to the PDL
ACTION: Motion to approve, 2nd, all in favor

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H. Spinal Muscular Atrophy Class Update and New Drug Evaluation
Recommendation: add the class to the PDL and designate Zolgensma as preferred and nusinersen non-preferred
ACTION: Motion to approve, 2nd, all in favor

I. Bone Metabolism Drugs Class Update and New Drug Evaluation
Recommendation: make no changes to the PDL
ACTION: Motion to approve, 2nd, all in favor

VI. ADJOURN

VII. OHA RULES ADVISORY COMMITTEE

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Pharmacy Utilization Summary Report: April 2018 - March 2019

Eligibility	Apr-18	May-18	Jun-18	Jul-18	Aug-18	Sep-18	Oct-18	Nov-18	Dec-18	Jan-19	Feb-19	Mar-19	Avg Monthly
Total Members (FFS & Encounter)	965,503	964,592	965,132	962,205	964,077	963,131	964,428	966,366	965,956	970,009	973,211	979,795	967,034
FFS Members	121,038	113,512	117,714	120,682	119,156	121,522	115,577	120,900	125,681	118,919	119,390	125,420	119,959
OHP Basic with Medicare	34,378	34,471	34,742	34,887	35,039	35,293	35,249	35,494	35,531	33,066	33,109	33,374	34,553
OHP Basic without Medicare	12,207	11,665	11,817	11,917	11,827	11,956	11,702	11,714	11,824	11,916	11,789	11,811	11,845
ACA	74,453	67,376	71,155	73,878	72,290	74,273	68,626	73,692	78,326	73,937	74,492	80,235	73,561
Encounter Members	844,465	851,080	847,418	841,523	844,921	841,609	848,851	845,466	840,275	851,090	853,821	854,375	847,075
OHP Basic with Medicare	41,143	41,324	41,337	41,300	41,375	41,334	41,471	41,476	41,372	43,801	43,841	43,822	41,966
OHP Basic without Medicare	63,126	63,424	63,149	62,869	62,744	62,264	62,281	62,113	61,913	61,991	61,974	61,949	62,483
ACA	740,196	746,332	742,932	737,354	740,802	738,011	745,099	741,877	736,990	745,298	748,006	748,604	742,625

Gross Cost Figures for Drugs	Apr-18	May-18	Jun-18	Jul-18	Aug-18	Sep-18	Oct-18	Nov-18	Dec-18	Jan-19	Feb-19	Mar-19	YTD Sum
Total Amount Paid (FFS & Encounter)	$74,879,487	$77,986,150	$73,154,408	$74,469,354	$78,426,143	$69,121,306	$79,385,906	$73,730,116	$70,707,434	$80,156,807	$72,177,317	$79,486,119	$903,680,547
Mental Health Carve-Out Drugs	$7,640,898	$7,953,178	$7,578,826	$7,681,936	$7,925,006	$7,131,943	$8,140,645	$7,653,489	$7,527,733	$8,171,510	$7,365,314	$7,868,712	$92,639,189
OHP Basic with Medicare	$2,647	$1,101	$61	$4,472	$6,085	$4,293	$5,584	$4,637	$5,502	$8,243	$6,479	$5,197	$54,301
OHP Basic without Medicare	$3,205,527	$3,346,398	$3,223,881	$3,198,935	$3,332,998	$2,944,414	$3,384,208	$3,134,299	$3,111,921	$3,308,641	$2,985,357	$3,107,705	$38,284,284
ACA	$4,377,222	$4,553,317	$4,303,058	$4,424,469	$4,523,547	$4,131,761	$4,694,639	$4,453,745	$4,356,778	$4,791,992	$4,308,396	$4,690,085	$53,609,009
FFS Physical Health Drugs	$2,906,561	$2,998,618	$2,744,619	$2,795,885	$3,070,573	$2,496,881	$3,067,676	$2,656,680	$2,671,405	$3,149,402	$2,626,449	$2,865,784	$34,050,532
OHP Basic with Medicare	$240,637	$274,476	$227,045	$228,289	$237,203	$213,639	$292,151	$244,512	$240,948	$255,504	$219,960	$256,815	$2,931,178
OHP Basic without Medicare	$932,939	$1,010,864	$855,937	$822,590	$962,048	$717,431	$936,473	$814,787	$777,924	$1,027,411	$877,307	$954,154	$10,689,866
ACA	$1,582,807	$1,574,586	$1,530,063	$1,612,928	$1,703,504	$1,443,960	$1,713,568	$1,467,738	$1,528,644	$1,743,900	$1,416,768	$1,540,215	$18,858,680
FFS Physician Administered Drugs	$1,513,655	$1,656,752	$1,663,556	$1,490,104	$1,725,075	$1,421,266	$1,824,048	$1,524,818	$1,331,497	$1,907,248	$1,944,139	$1,771,581	$19,773,739
OHP Basic with Medicare	$425,638	$482,619	$425,132	$342,740	$452,271	$413,505	$409,269	$454,720	$325,806	$562,381	$499,391	$502,057	$5,295,528
OHP Basic without Medicare	$104,619	$306,643	$388,681	$275,453	$386,587	$217,657	$601,357	$134,677	$129,854	$323,648	$519,666	$224,282	$3,613,124
ACA	$402,340	$504,608	$482,970	$500,423	$577,322	$482,348	$467,613	$581,539	$548,550	$609,091	$539,357	$592,448	$6,288,610
Encounter Physical Health Drugs	$51,507,695	$53,607,096	$50,458,295	$50,301,802	$53,185,293	$47,493,805	$54,162,684	$50,037,949	$48,440,989	$53,523,565	$48,765,001	$54,646,140	$616,130,314
OHP Basic with Medicare	$130,839	$139,073	$126,535	$190,629	$271,154	$228,582	$263,143	$235,633	$248,624	$321,140	$266,895	$307,651	$2,729,899
OHP Basic without Medicare	$13,405,825	$13,921,106	$13,287,931	$13,360,638	$14,029,267	$12,444,517	$14,204,887	$13,152,043	$12,794,811	$13,541,332	$11,981,799	$13,356,731	$159,480,886
ACA	$37,244,456	$38,827,393	$36,426,688	$36,131,663	$38,207,648	$34,144,500	$39,053,668	$36,030,187	$34,821,113	$38,889,297	$35,825,501	$40,310,576	$445,912,691
Encounter Physician Administered Drugs	$11,310,677	$11,770,507	$10,709,112	$12,199,627	$12,520,196	$10,577,411	$12,190,852	$11,857,180	$10,735,810	$13,405,082	$11,476,414	$12,333,903	$141,086,773
OHP Basic with Medicare	$256,239	$241,167	$215,682	$243,150	$253,535	$202,958	$264,925	$259,088	$227,430	$385,087	$291,402	$268,309	$3,108,972
OHP Basic without Medicare	$2,721,949	$2,707,835	$2,271,992	$2,993,207	$2,844,298	$2,550,513	$2,786,741	$2,690,707	$2,436,954	$2,879,729	$2,739,427	$2,779,997	$32,403,350
ACA	$8,151,793	$8,540,919	$8,094,146	$8,710,216	$9,294,491	$7,696,351	$8,946,587	$8,781,121	$7,937,105	$9,955,173	$8,317,413	$9,119,302	$103,544,617

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: October 17, 2019

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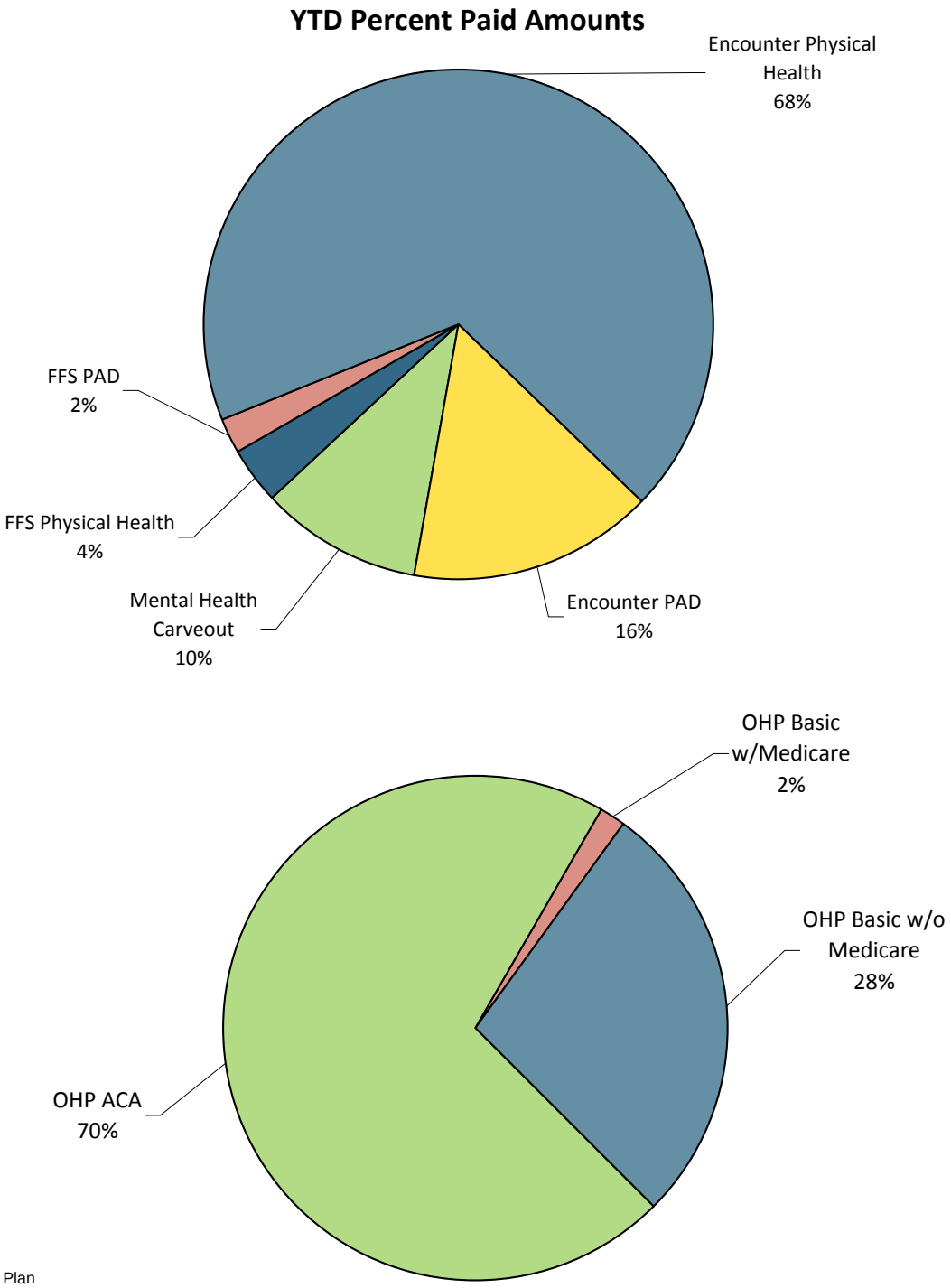
Pharmacy Utilization Summary Report: April 2018 - March 2019



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

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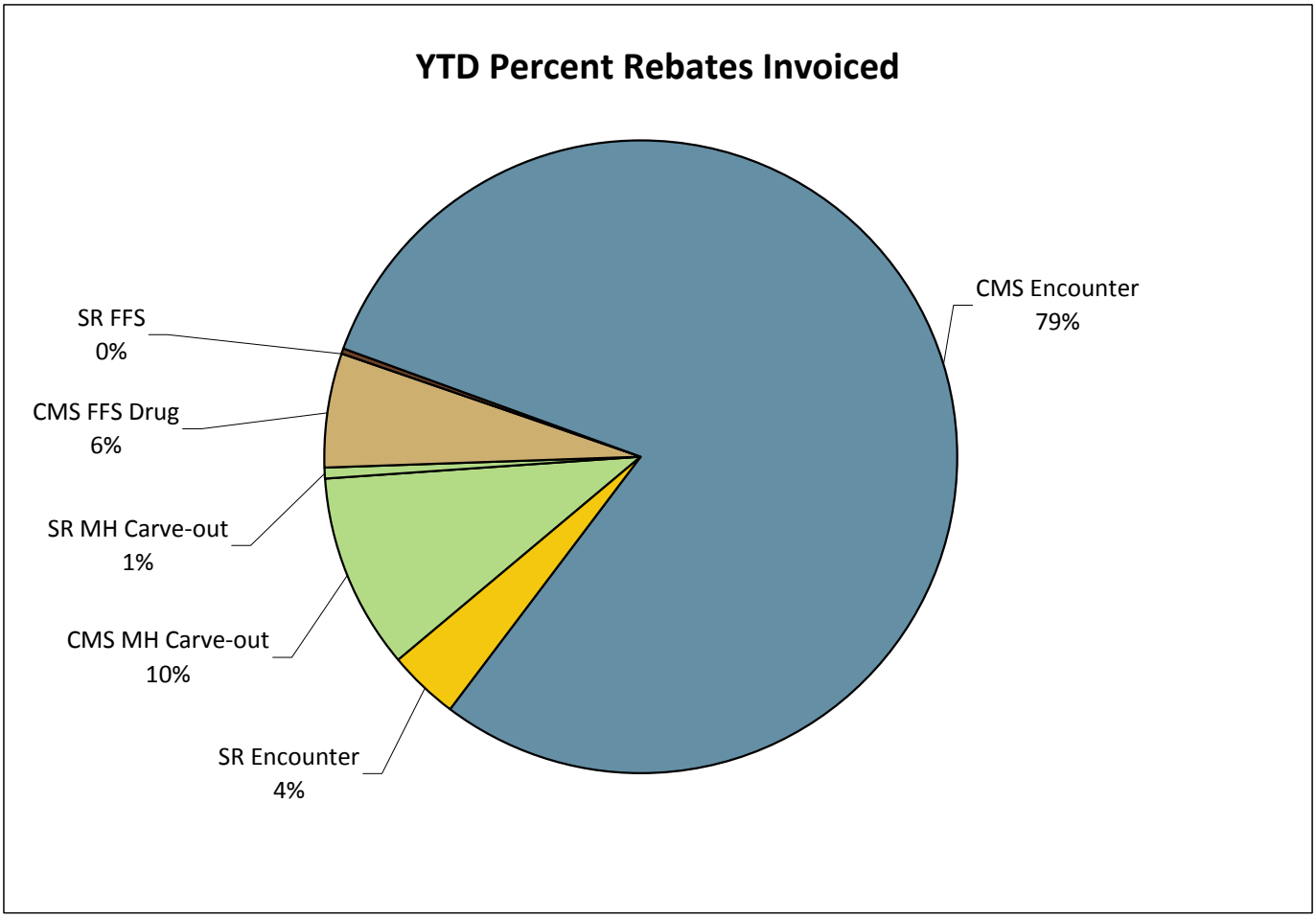
Pharmacy Utilization Summary Report: April 2018 - March 2019

Quarterly Rebates Invoiced	2018-Q2	2018-Q3	2018-Q4	2019-Q1	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$107,516,201	$103,759,672	$101,254,785	$102,241,584	$414,772,242
CMS MH Carve-out	$9,973,227	$9,906,546	$10,078,468	$11,229,498	$41,187,739
SR MH Carve-out	$559,564	$573,570	$654,824	$1,065,577	$2,853,535
CMS FFS Drug	$6,406,741	$6,144,046	$5,437,155	$6,343,616	$24,331,558
SR FFS	$229,770	$266,734	$256,998	$272,382	$1,025,884
CMS Encounter	$86,653,902	$83,472,134	$81,479,881	$78,611,284	$330,217,201
SR Encounter	$3,692,998	$3,396,643	$3,347,458	$4,719,227	$15,156,326

Quaterly Net Drug Costs	2018-Q2	2018-Q3	2018-Q4	2019-Q1	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$118,503,844	$118,257,130	$122,568,671	$129,578,659	$488,908,305
Mental Health Carve-Out Drugs	$12,640,112	$12,258,769	$12,588,573	$11,110,461	$48,597,916
FFS Phys Health + PAD	$6,847,249	$6,589,004	$7,381,972	$7,648,604	$28,466,829
Encounter Phys Health + PAD	$99,016,483	$99,409,357	$102,598,126	$110,819,594	$411,843,560



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

Last Updated: October 17, 2019

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Pharmacy Utilization Summary Report: April 2018 - March 2019

Gross PMPM Drug Costs (Rebates not Subtracted)	Apr-18	May-18	Jun-18	Jul-18	Aug-18	Sep-18	Oct-18	Nov-18	Dec-18	Jan-19	Feb-19	Mar-19	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$77.55	$80.85	$75.80	$77.39	$81.35	$71.77	$82.31	$76.30	$73.20	$82.64	$74.16	$81.13	$77.87
Mental Health Carve-Out Drugs	$7.91	$8.25	$7.85	$7.98	$8.22	$7.40	$8.44	$7.92	$7.79	$8.42	$7.57	$8.03	$7.98
FFS Physical Health Drugs	$24.01	$26.42	$23.32	$23.17	$25.77	$20.55	$26.54	$21.97	$21.26	$26.48	$22.00	$22.85	$23.69
FFS Physician Administered Drugs	$12.51	$14.60	$14.13	$12.35	$14.48	$11.70	$15.78	$12.61	$10.59	$16.04	$16.28	$14.13	$13.77
Encounter Physical Health Drugs	$60.99	$62.99	$59.54	$59.77	$62.95	$56.43	$63.81	$59.18	$57.65	$62.89	$57.11	$63.96	$60.61
Encounter Physician Administered Drugs	$13.39	$13.83	$12.64	$14.50	$14.82	$12.57	$14.36	$14.02	$12.78	$15.75	$13.44	$14.44	$13.88

Claim Counts	Apr-18	May-18	Jun-18	Jul-18	Aug-18	Sep-18	Oct-18	Nov-18	Dec-18	Jan-19	Feb-19	Mar-19	Avg Monthly
Total Claim Count (FFS & Encounter)	1,034,996	1,073,745	1,005,803	1,005,461	1,038,604	962,420	1,072,173	1,005,954	990,915	1,080,391	962,849	1,052,506	1,023,818
Mental Health Carve-Out Drugs	153,897	159,425	149,619	152,701	157,433	144,518	161,716	152,603	150,643	163,411	145,290	156,634	153,991
FFS Physical Health Drugs	59,171	60,043	56,168	55,385	57,671	52,446	58,559	54,949	53,773	60,162	53,668	58,642	56,720
FFS Physician Administered Drugs	14,380	15,195	14,261	14,810	15,624	14,120	15,044	13,493	13,673	15,289	12,674	13,683	14,354
Encounter Physical Health Drugs	701,026	727,758	680,816	674,579	697,494	648,528	723,918	679,578	668,518	729,037	650,843	712,729	691,235
Encounter Physician Administered Drugs	106,522	111,324	104,939	107,986	110,382	102,808	112,936	105,331	104,308	112,492	100,374	110,818	107,518

Gross Amount Paid per Claim (Rebates not Subtracted)	Apr-18	May-18	Jun-18	Jul-18	Aug-18	Sep-18	Oct-18	Nov-18	Dec-18	Jan-19	Feb-19	Mar-19	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$72.35	$72.63	$72.73	$74.06	$75.51	$71.82	$74.04	$73.29	$71.36	$74.19	$74.96	$75.52	$73.54
Mental Health Carve-Out Drugs	$49.65	$49.89	$50.65	$50.31	$50.34	$49.35	$50.34	$50.15	$49.97	$50.01	$50.69	$50.24	$50.13
FFS Physical Health Drugs	$49.12	$49.94	$48.86	$50.48	$53.24	$47.61	$52.39	$48.35	$49.68	$52.35	$48.94	$48.87	$49.99
FFS Physician Administered Drugs	$105.26	$109.03	$116.65	$100.61	$110.41	$100.66	$121.25	$113.01	$97.38	$124.75	$153.40	$129.47	$115.16
Encounter Physical Health Drugs	$73.47	$73.66	$74.11	$74.57	$76.25	$73.23	$74.82	$73.63	$72.46	$73.42	$74.93	$76.67	$74.27
Encounter Physician Administered Drugs	$106.18	$105.73	$102.05	$112.97	$113.43	$102.89	$107.94	$112.57	$102.92	$119.16	$114.34	$111.30	$109.29

Gross Amount Paid per Claim - Generic-Multi Source Drugs (Rebates not Subtracted)	Apr-18	May-18	Jun-18	Jul-18	Aug-18	Sep-18	Oct-18	Nov-18	Dec-18	Jan-19	Feb-19	Mar-19	Avg Monthly
Generic-Multi Source Drugs: Average Paid / Claim (FFS & Encounter)	$19.46	$19.34	$19.21	$19.10	$19.09	$18.80	$18.25	$18.03	$18.08	$18.31	$19.44	$19.57	$18.89
Mental Health Carve-Out Drugs	$20.71	$20.80	$20.91	$20.96	$20.77	$19.38	$19.52	$19.50	$18.47	$18.03	$18.18	$17.49	$19.56
FFS Physical Health Drugs	$16.46	$16.49	$16.47	$16.27	$16.20	$16.15	$16.42	$16.66	$15.89	$16.63	$16.85	$17.47	$16.50
Encounter Physical Health Drugs	$19.36	$19.18	$18.98	$18.81	$18.86	$18.84	$18.05	$17.74	$18.13	$18.50	$19.95	$20.23	$18.89

0

Gross Amount Paid per Claim - Branded-Single Source Drugs (Rebates not Subtracted)	Apr-18	May-18	Jun-18	Jul-18	Aug-18	Sep-18	Oct-18	Nov-18	Dec-18	Jan-19	Feb-19	Mar-19	Avg Monthly
Branded-Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$342.83	$348.49	$348.99	$360.22	$361.51	$337.95	$348.17	$356.72	$356.71	$365.89	$405.21	$448.96	$365.14
Mental Health Carve-Out Drugs	$992.86	$989.77	$1,011.18	$998.60	$992.35	$1,003.95	$1,016.60	$1,013.80	$1,021.23	$1,031.57	$1,041.37	$1,045.95	$1,013.27
FFS Physical Health Drugs	$137.66	$140.86	$136.70	$144.85	$152.06	$132.80	$152.15	$141.49	$149.13	$162.45	$154.01	$163.14	$147.28
Encounter Physical Health Drugs	$345.35	$350.86	$351.08	$362.48	$363.84	$337.69	$345.79	$355.92	$353.81	$362.16	$407.56	$455.84	$366.03

0

Generic Drug Use Percentage	Apr-18	May-18	Jun-18	Jul-18	Aug-18	Sep-18	Oct-18	Nov-18	Dec-18	Jan-19	Feb-19	Mar-19	Avg Monthly
Generic Drug Use Percentage	85.0%	85.2%	85.0%	85.4%	85.0%	84.7%	84.5%	85.2%	85.5%	85.7%	87.1%	88.1%	85.6%
Mental Health Carve-Out Drugs	97.0%	97.0%	97.0%	97.0%	97.0%	97.0%	96.9%	96.9%	96.9%	96.8%	96.8%	96.8%	96.9%
FFS Physical Health Drugs	73.1%	73.1%	73.1%	73.4%	72.7%	73.0%	73.5%	74.6%	74.6%	75.5%	76.6%	78.4%	74.3%
Encounter Physical Health Drugs	83.4%	83.6%	83.4%	83.8%	83.4%	82.9%	82.7%	83.5%	83.8%	84.0%	85.8%	87.0%	83.9%

Preferred Drug Use Percentage	Apr-18	May-18	Jun-18	Jul-18	Aug-18	Sep-18	Oct-18	Nov-18	Dec-18	Jan-19	Feb-19	Mar-19	Avg Monthly
Preferred Drug Use Percentage	86.63%	86.73%	86.57%	86.41%	86.21%	86.07%	85.89%	85.82%	85.82%	85.82%	85.72%	85.72%	86.1%
Mental Health Carve-Out Drugs	74.18%	74.24%	73.93%	74.05%	73.87%	73.89%	73.82%	73.63%	73.67%	74.13%	73.91%	73.65%	73.9%
FFS Physical Health Drugs	95.54%	95.46%	95.76%	95.63%	95.76%	95.85%	95.68%	95.84%	95.80%	95.50%	95.44%	95.53%	95.6%
Encounter Physical Health Drugs	88.62%	88.75%	88.58%	88.44%	88.19%	88.02%	87.83%	87.77%	87.78%	87.66%	87.59%	87.59%	88.1%

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: October 17, 2019

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Top 40 Drugs by Gross Amount Paid (FFS Only) - Third Quarter 2019

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	LATUDA	Antipsychotics, 2nd Gen	$5,731,973	16.2%	4,793	$1,196	Y
2	INVEGA SUSTENNA	Antipsychotics, Parenteral	$2,764,082	7.8%	1,439	$1,921	Y
3	ABILIFY MAINTENA	Antipsychotics, Parenteral	$1,482,379	4.2%	763	$1,943	Y
4	REXULTI	Antipsychotics, 2nd Gen	$1,398,575	4.0%	1,276	$1,096	V
5	VRAYLAR	Antipsychotics, 2nd Gen	$1,290,609	3.7%	1,132	$1,140	Y
6	INVEGA TRINZA	Antipsychotics, Parenteral	$717,059	2.0%	122	$5,878	Y
7	BUPROPION XL	Antidepressants	$557,123	1.6%	25,883	$22	V
8	TRINTELLIX	Antidepressants	$532,987	1.5%	1,387	$384	V
9	FLUOXETINE HCL	Antidepressants	$528,211	1.5%	33,662	$16	Y
10	SAPHRIS	Antipsychotics, 2nd Gen	$473,458	1.3%	735	$644	Y
11	SERTRALINE HCL	Antidepressants	$451,124	1.3%	44,775	$10	Y
12	PALIPERIDONE ER	Antipsychotics, 2nd Gen	$449,322	1.3%	1,753	$256	V
13	VIIBRYD	Antidepressants	$445,951	1.3%	1,600	$279	V
14	DULOXETINE HCL	Antidepressants	$434,086	1.2%	30,989	$14	V
15	TRAZODONE HCL	Antidepressants	$396,237	1.1%	38,977	$10	
16	ATOMOXETINE HCL*	ADHD Drugs	$388,627	1.1%	5,524	$70	Y
17	ARISTADA	Antipsychotics, Parenteral	$351,463	1.0%	170	$2,067	Y
18	VENLAFAXINE HCL ER	Antidepressants	$349,995	1.0%	2,047	$171	V
19	RISPERDAL CONSTA*	Antipsychotics, Parenteral	$349,318	1.0%	410	$852	Y
20	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$333,799	0.9%	28	$11,921	Y
21	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	$277,144	0.8%	18,603	$15	
22	LAMOTRIGINE ER	Antiepileptics (oral & rectal)	$268,184	0.8%	2,069	$130	V
23	ESCITALOPRAM OXALATE	Antidepressants	$262,944	0.7%	26,348	$10	Y
24	LAMOTRIGINE	Antiepileptics (oral & rectal)	$238,637	0.7%	23,448	$10	Y
25	ARIPIPRAZOLE	Antipsychotics, 2nd Gen	$231,980	0.7%	14,728	$16	V
26	CONCERTA*	ADHD Drugs	$227,229	0.6%	880	$258	N
27	CHOLBAM*	Bile Therapy	$224,129	0.6%	3	$74,710	
28	BIKTARVY	HIV	$215,134	0.6%	84	$2,561	Y
29	AMITRIPTYLINE HCL	Antidepressants	$210,253	0.6%	14,382	$15	Y
30	Inj., Emicizumab-Kxwh 0.5 Mg	Physican Administered Drug	$191,976	0.5%	7	$27,425	
31	VENLAFAXINE HCL ER	Antidepressants	$188,096	0.5%	14,898	$13	Y
32	CITALOPRAM HBR	Antidepressants	$187,751	0.5%	21,271	$9	Y
33	QUETIAPINE FUMARATE*	Antipsychotics, 2nd Gen	$184,002	0.5%	15,931	$12	Y
34	Inj, Nusinersen, 0.1mg	Physican Administered Drug	$174,385	0.5%	1	$174,385	
35	LANTUS SOLOSTAR*	Diabetes, Insulins	$173,176	0.5%	497	$348	Y
36	Factor Viii Pegylated Recomb	Physican Administered Drug	$159,205	0.5%	3	$53,068	
37	WELLBUTRIN XL	Antidepressants	$148,514	0.4%	128	$1,160	V
38	FETZIMA	Antidepressants	$147,919	0.4%	383	$386	V
39	ORKAMBI*	Cystic Fibrosis	$146,653	0.4%	13	$11,281	N
40	BUPROPION HCL SR	Antidepressants	$145,746	0.4%	10,012	$15	Y
		Top 40 Aggregate:	**$23,429,436**		**361,154**	**$9,393**	
		All FFS Drugs Totals:	**$35,307,714**		**624,823**	**$587**	

*** 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: October 17, 2019

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

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$333,799	3.3%	28	$11,921	Y
2	CONCERTA*	ADHD Drugs	$227,229	2.2%	880	$258	N
3	CHOLBAM*	Bile Therapy	$224,129	2.2%	3	$74,710	
4	BIKTARVY	HIV	$215,134	2.1%	84	$2,561	Y
5	Inj., Emicizumab-Kxwh 0.5 Mg	Physican Administered Drug	$191,976	1.9%	7	$27,425	
6	Inj, Nusinersen, 0.1mg	Physican Administered Drug	$174,385	1.7%	1	$174,385	
7	LANTUS SOLOSTAR*	Diabetes, Insulins	$173,176	1.7%	497	$348	Y
8	Factor Viii Pegylated Recomb	Physican Administered Drug	$159,205	1.6%	3	$53,068	
9	ORKAMBI*	Cystic Fibrosis	$146,653	1.4%	13	$11,281	N
10	NOVOLOG FLEXPEN	Diabetes, Insulins	$125,237	1.2%	255	$491	Y
11	Etonogestrel Implant System	Physican Administered Drug	$113,107	1.1%	177	$639	
12	LANTUS	Diabetes, Insulins	$108,176	1.1%	322	$336	Y
13	Injection, Pegfilgrastim 6mg	Physican Administered Drug	$105,827	1.0%	32	$3,307	
14	NUVARING	STC 63 - Oral Contraceptives	$103,809	1.0%	378	$275	
15	ALBUTEROL SULFATE HFA	Beta-Agonists, Inhaled Short-Acting	$101,819	1.0%	2,316	$44	Y
16	ENBREL SURECLICK*	Biologics for Autoimmune Conditions	$101,700	1.0%	30	$3,390	Y
17	VYVANSE*	ADHD Drugs	$98,674	1.0%	673	$147	Y
18	BUPRENORPHINE-NALOXONE*	Substance Use Disorders, Opioid & Alcohol	$93,979	0.9%	1,524	$62	Y
19	Epoetin Alfa, 100 Units Esrd	Physican Administered Drug	$87,884	0.9%	486	$181	
20	Bevacizumab Injection	Physican Administered Drug	$87,494	0.9%	87	$1,006	
21	Mirena, 52 Mg	Physican Administered Drug	$85,553	0.8%	134	$638	
22	FLOVENT HFA	Corticosteroids, Inhaled	$85,534	0.8%	524	$163	Y
23	CHANTIX*	Tobacco Smoking Cessation	$81,510	0.8%	219	$372	Y
24	HYDROXYPROGESTERONE CAPROAT	Progestational Agents	$78,682	0.8%	29	$2,713	N
25	ELIQUIS	Anticoagulants, Oral and SQ	$78,513	0.8%	229	$343	Y
26	TECFIDERA*	Multiple Sclerosis	$74,494	0.7%	14	$5,321	N
27	VIGABATRIN	Antiepileptics (oral & rectal)	$73,447	0.7%	7	$10,492	N
28	EPCLUSA*	Hepatitis C, Direct-Acting Antivirals	$72,966	0.7%	3	$24,322	Y
29	Infliximab Not Biosimil 10mg	Physican Administered Drug	$72,002	0.7%	59	$1,220	
30	Pegaspargase Injection	Physican Administered Drug	$71,321	0.7%	3	$23,774	
31	XIFAXAN*	Rifamycins	$71,050	0.7%	33	$2,153	
32	Inj Trastuzumab Excl Biosimi	Physican Administered Drug	$66,428	0.6%	33	$2,013	
33	VIMPAT	Antiepileptics (oral & rectal)	$66,090	0.6%	167	$396	Y
34	SYMBICORT	Corticosteroids/LABA Combination, Inhaled	$64,229	0.6%	271	$237	Y
35	SPIRIVA	Anticholinergics, Inhaled	$63,379	0.6%	172	$368	Y
36	Inj Pembrolizumab	Physican Administered Drug	$62,979	0.6%	43	$1,465	
37	XULANE	STC 63 - Oral Contraceptives	$62,591	0.6%	374	$167	
38	GENVOYA	HIV	$62,498	0.6%	25	$2,500	Y
39	TRUVADA	HIV	$62,008	0.6%	57	$1,088	Y
40	Inj., Rituximab, 10 Mg	Physican Administered Drug	$60,926	0.6%	47	$1,296	
		Top 40 Aggregate:	**$4,389,593**		**10,239**	**$11,172**	
		All FFS Drugs Totals:	**$10,229,752**		**145,806**	**$605**	

*** 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: October 17, 2019

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Drug Class Update: Antifungals (oral and topical)

Month/Year of Review: November 2019

Date of Last Review: September 2014 (topical)
July 2015 (oral)
Literature Search: 07/15/14 – 08/15/19

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

Purpose for Class Update: The purpose of this update is to review and evaluate new high-quality literature that has been published since the last review on oral and topical antifungal therapies as well as evaluate appropriateness of current policy and preferred drug list (PDL) placement.

Research Questions:
- Is there any new comparative evidence related to efficacy for the oral or topical antifungals for important outcomes (e.g., clinical cure or mortality)?
- Is there any new comparative evidence based on harms outcomes for the oral or topical antifungals?
- Are there any subpopulations which would receive more benefit or suffer more harm from specific oral or topical antifungals?

Conclusions:
- Four systematic reviews and meta-analyses, five guidelines and one randomized trial are included in this update.
- The risk of developing and risk of dying from cryptococcal disease was reduced with primary prophylaxis antifungal therapy, itraconazole or fluconazole, in human immunodeficiency virus (HIV)-positive individuals at high risk of developing cryptococcal disease based on moderate quality evidence from one Cochrane review.[1]
- Evidence for the use of topical antifungals for seborrheic dermatitis was insufficient to draw strong conclusions regarding efficacy or safety.[2]
- One fair-quality trial found isavuconazole to be noninferior to voriconazole for the outcome of mortality at day 42 when used in patients with invasive mold disease caused by aspergillosis or other filamentous fungi.[3]
- Guidance for the treatment of opportunistic infections in adult and adolescent patients with HIV, guidelines on the management of aspergillosis, clinical practice guideline for the treatment of coccidioidomycosis, guidance on the management of candidiasis, and prevention and treatment of cancer-related infections supports current antifungal preferred drug list (PDL) placement.[4,5,6,7,8]
- There is insufficient evidence on benefits or harms of antifungals in subpopulations.

Recommendations:
- No changes to the PDL are recommended based on a review of the clinical safety and efficacy evidence.
- Evaluate costs in executive session.

Author: Kathy Sentena, PharmD

Summary of Prior Reviews and Current Policy

- Previous reviews have not found clinically significant differences in efficacy or harms between the different oral antifungals.
- Prior authorization is required for griseofulvin, itraconazole, and terbinafine due to limited usage beyond onychomycosis, which is unfunded.
- Use of voriconazole is authorized for use by hematologists, oncologists and infectious disease without restriction to allow for coverage of invasive aspergillosis.
- Evidence does not support differences in harms or adverse events between the oral antifungals with the exception of ketoconazole which has been associated with hepatotoxicity, adrenal insufficiency and drug interactions.
- There is no evidence of clinically significant differences in efficacy or harms between the topical antifungal treatments.
- The Oregon Health Plan list of prioritized services does not fund treatment for candidiasis of mouth, skin and nails or dermatophytosis of nail, groin, scalp and foot and other dermatomycosis in immune-competent hosts. Topical antifungal agents are solely indicated for these and other related non-funded conditions.
- Financial impact of this class is minimal to the Oregon Health Plan (OHP) and there was 98% utilization of preferred oral antifungals and 83% of preferred topical therapies in the second quarter of 2019.

Background:

The antifungal class covers treatment of life-threatening illnesses, such as invasive aspergillosis, to unfunded cosmetic diagnoses such as toenail onychomycosis. Serious fungal infections are usually seen in individuals with compromised immune systems, such as prolonged neutropenia, allogenic hematopoietic stem cell transplant and acquired immunodeficiencies requiring oral or intravenous antifungal therapy.[5] Topical antifungals are used for treatment of dermatophytes, yeasts and molds involving the skin, scalp, nails and mucous membrane. The most common skin infection is tinea pedis followed by tinea corporis and tinea capitis.[9] Important outcomes to determine antifungal efficacy include: symptom improvement, clinical cure (clinical symptoms), mycological cure (negative mycological test) and mortality.

Antifungals can be categorized as azoles, echinocandins, polyenes, allylamines and flucytosine.[10] Choice of antifungal depends on indication, causative organism and resistance patterns. Caspofungin, anidulafungin and micafungin are echinocandins with similar spectrum of action but differing dosing and drug interaction profiles. Echinocandins are most commonly used for serious fungal infections such as invasive candidiasis and as empiric therapy in patients with neutropenic fever.[11] Additionally, echinocandins have been used for salvage therapy in patients with invasive aspergillosis. Amphotericin deoxycholate, liposomal amphotericin and nystatin are polyene antifungals. Because high risk of nephrotoxicity is associated with systemic formulations of polyenes, these therapies are therefore designated as second-line options for invasive aspergillosis and candidiasis infections. Allylamine antifungals consist of naftifine and terbinafine. Flucytosine has antifungal properties that can be used in combination with amphotericin B for severe cryptococcal pneumonia and meningocephalitis, with a limited role in select invasive candidiasis infections. Due to high levels of resistance, flucytosine is not commonly used as monotherapy.[12] Drug interactions are common with antifungals and concomitant medications should be considered upon initiation.

Azole antifungals are categorized as either triazoles or imidazoles (e.g., fluconazole, itraconazole, voriconazole, posaconazole, isavuconazole and ketoconazole). The azole antifungals are effective in treating several types of fungal infections: candidiasis, aspergillosis, cryptococcosis, histoplasmosis, blastomycosis, and coccidioidomycosis. Fluconazole is most commonly recommended first-line for a majority of fungal infections due to efficacy and tolerability. Of the azole antifungals, posaconazole and isavuconazole have the broadest spectrum of action and are not associated with nephrotoxicity. There is wide variability in the bioavailability and types of drug interactions (highly metabolized via cytochrome P450 enzyme system) between the different antifungals. Gastrointestinal issues

are the most common adverse reactions associated with antifungal therapy and hepatic manifestations from mild elevations to hepatic failure have been demonstrated. For these reasons, transaminase monitoring is recommended for patients receiving extended treatment with antifungal therapy. Drug monitoring is a recommended for itraconazole, voriconazole, and posaconazole to ensure efficacy and avoid toxicity. For the initial treatment and salvage therapy triazole antifungals, such as voriconazole, are recommended for the treatment of aspergillosis.[5]

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. 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 – Primary Antifungal Prophylaxis for Cryptococcal Disease in HIV-positive People
A systematic review and meta-analysis of the efficacy and safety of primary prophylaxis for cryptococcal disease in people who are HIV-positive was completed in 2018.[1] Patients were considered at high risk of cryptococcal disease with low cluster of differentiation 4 (CD4) cell counts. A total of nine trials, six of which were placebo controlled, met the inclusion criteria. Treatments included the antifungals itraconazole and fluconazole. Only two of the trials were conducted after the introduction of modern HIV treatments.[1] Overall the risk of bias was low for most of the trials for most of the domains.

Primary prophylaxis with antifungal therapy did not provide a conclusive all-cause mortality benefit due to the low quality of evidence. The risk of developing cryptococcal disease was reduced with antifungal therapy compared to placebo (RR 0.29; 95% CI, 0.17 to 0.49) based on moderate evidence. This finding equates to 30 per 1000 patients at risk of cryptococcal disease compared to 9 per 1000 patients receiving antifungal prophylaxis.[1] The risk of mortality due to cryptococcal disease was reduced in patient receiving antifungal prophylaxis from 3 per 1000 people treated with antifungals to 11 per 1000 people in those not receiving prophylaxis (RR 0.29; 95% CI, 0.11 to 0.72).[1] There was moderate evidence that of no difference in the discontinuation rates between antifungals and placebo. In conclusion, there was a benefit of primary prophylaxis with antifungals in patients at high risk of cryptococcal disease compared to placebo and in patients not receiving modern HIV treatment.

Cochrane – Topical Antifungals for Seborrhoeic Dermatitis
A 2015 Cochrane review evaluated the efficacy and safety of the use of topical antifungals for seborrhoeic dermatitis. Fifty-one studies of adolescents and adults (n=9052) were included. Most trial durations were five weeks or less and evaluated the following antifungals: ketoconazole (usually 2%), ciclopirox, lithium, bifonazole (not available in the US) and clotrimazole.

Most of the evidence for antifungal use in the treatment of seborrhoeic dermatitis is of low or very low quality due to the availability of only a few small studies. The use of topical ketoconazole was associated with similar remission rates as topical steroids (low quality of evidence), however, the adverse events were 44% lower in the ketoconazole group (RR 0.56; 95% CI, 0.32 to 0.96; number needed to benefit [NNTB] 3).[2] In general ketoconazole was more effective than placebo in reducing erythema and clearance of scaling; however, results could not be pooled. Results for ketoconazole compared to placebo were similar when studies with and without conflict of interest were analyzed separately. The use of topical ciclopirox 1% resulted in a reduction in the number of failed remissions compared to placebo at four weeks based on data from eight studies, 66% versus 79% (RR 0.79; 95% CI, 0.67 to 0.94), and adverse reactions were similar between therapies (moderate evidence).[2] In conclusion, there is insufficient evidence to draw strong conclusions on comparative efficacy or safety for the use of topical antifungals for seborrhoeic dermatitis.

After review, 7 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:
High Quality Guidelines:

Centers for Disease Control, National Institutes of Health, Human Immunodeficiency Virus Medicine Association of the Infectious Disease Society of America – Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV
An updated version of guidance for managing opportunistic infections in patients with HIV was released in October of 2017.[4] The guidelines include a comprehensive review of preventing and treating a multitude of infections; however, this review will focus on diseases in which antifungals are indicated. Recommendations are included for the management of candidiasis (mucocutaneous), coccidioidomycosis, and cryptococcosis. Recommendations are based on a systematic review of the literature with subsequent determination of the strength of the recommendation and quality of evidence used for the recommendation and are presented in **Table 1**.[13]

Table 1. Recommendation Strength and Quality Definitions[4]

Strength of Recommendation	Quality of Evidence for the Recommendation
A: Strong recommendation for the statement	I: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
B: Moderate recommendation for the statement	II: One or more well-designed, non-randomized trials or observational cohort studies with long-term clinical outcomes
C: Optional recommendation for the statement	III: Expert opinion

Recommendations for antifungal treatment are indication dependent (**Table 2**).[4] Oral fluconazole is the drug of choice for oropharyngeal candidiasis and esophageal candidiasis based on fungal clearance rates and lower recurrence rate. Oral fluconazole is also recommended first-line for vulvovaginal candidiasis. In treatment-resistant cases of mucocutaneous candidiasis, posaconazole oral suspension (AI), oral itraconazole (BII), anidulafungin (BII), caspofungin (BII), micafungin (BII), voriconazole (BII) or amphotericin B (BII) can be used.[4] If secondary prophylaxis (i.e., maintenance/supressive therapy) is indicated, oral fluconazole or posaconazole therapy are recommended. Topical therapy is recommended for patients who are pregnant (AIII), as systemic antifungal treatments range from pregnancy category B to X. Treatment of coccidioidomycosis can usually be treated with an oral triazole antifungal. Due to high relapse rates of approximately 80% of patients with coccidioidal meningitis, life-long antifungal therapy is indicated. For patients that are pregnant with non-meningeal

coccidioidomycosis, amphotericin B, deoxycholate or lipid preparation are recommended (AIII). Systemic azole antifungals should be avoided in the first trimester of pregnancy (BIII).[4]

Table 2. Antifungal Treatment Recommendations for Opportunistic Infections in Patients with HIV[4]

Indication for Therapy	Recommendation	Strength of Evidence
Oropharyngeal Candidiasis Duration of therapy: 7-14 days	Fluconazole 100 mg tablets or solution once daily*	AI
	Miconazole 50 mg mucoadhesive buccal tablets once daily	BI
	Clotrimazole troches 10 mg five times a day	BI
	Nystatin suspension or pastilles four times daily	BII
	Itraconazole 200 mg oral solution daily	BI
	Posaconazole 400 mg oral suspension twice daily for one day and then 400 mg daily	BI
Esophageal disease Duration of therapy: 14-21 days	Fluconazole 100 mg (up to 400 mg) once daily (oral or IV)*	AI
	Itraconazole oral solution 200 mg daily*	AI
	Oral itraconazole capsules (capsules not recommended due to variable absorption)	CII
	Isavuconazole 200 mg orally as a loading dose, followed by 50 mg daily	BI
	Isavuconazole 400 mg orally as a loading dose, followed by 100 mg daily	B1
	Isavuconazole 400 mg orally once weekly	BI
	Voriconazole 200 mg PO or IV twice daily	BI
	Amphotericin B deoxycholate IV daily	BI
	Lipid formulation of amphotericin B IV daily	BIII
	Echinocandins (caspofungin, micafungin, and anidulafungin) (doses not provided)	BI
Vulvovaginal Candidiasis Duration of therapy: fluconazole – 1 day, all others 3-7 days	Oral fluconazole 150 mg for one dose*	AII
	Topical azoles (i.e., clotrimazole, butoconazole, miconazole, tioconazole, or terconazole)*	AII
	Itraconazole 200 mg oral solution	BII
Coccidioidomycosis Duration of therapy: depends on response Mild infections	Fluconazole 400 mg daily*	BII
	Itraconazole 200 mg twice daily*	BII
	Voriconazole 200 mg twice daily, after loading dose of 400 mg twice daily	BIII
	Posaconazole 300 mg delayed release tablets after loading dose of 300 mg twice daily for one day	BIII
	Posaconazole oral suspension 400 mg orally twice daily	BII
Bone or joint infections	Itraconazole 200 mg orally twice daily*	AI
	Fluconazole 400 mg orally once daily	BI
Severe infections	Lipid formulation of amphotericin B IV*	AIII
	Amphotericin B deoxycholate IV*	AII
Meningeal Infection	Fluconazole 400-800 mg daily (oral or IV)*	AII
	Itraconazole 200 mg orally 2-3 times daily	BII

	Voriconazole 200-400 mg orally twice daily after loading dose	BIII
	Posaconazole delayed release tablet loading dose of 300 mg twice daily on day one and then 300 mg daily	CIII
	Posaconazole oral suspension 400 mg orally twice daily	CIII
	Intrathecal amphotericin B when triazole antifungals are not effective	AIII
Cryptococcosis Induction therapy Duration of therapy: at least 2 weeks	Liposomal amphotericin B IV plus flucytosine*	AI
	Amphotericin B deoxycholate IV plus flucytosine*	AI
	Amphotericin B lipid complex IV plus flucytosine	BII
	Liposomal amphotericin B IV plus fluconazole	BIII
	Amphotericin B (deoxycholate) IV plus fluconazole	BI
	Liposomal amphotericin B IV	BI
	Amphotericin B deoxycholate IV	BI
	Fluconazole 400 mg orally or IV plus flucytosine	BII
	Fluconazole 800 mg orally or IV plus flucytosine	BIII
	Fluconazole 1200 mg orally or IV	CI
Consolidation therapy Duration of therapy: at least 8 weeks	Fluconazole 400 mg orally or IV once daily*	AI
	Itraconazole 200 mg orally or IV twice daily	CI
Maintenance therapy Duration of therapy: at least 1 year and dependent upon response	Fluconazole 200 mg orally	AI
Non-CNS cryptococococcosis focal pulmonary disease and isolated cryptococcal antigenemia Duration of treatment: 12 months	Fluconazole 400 mg orally	BIII
Key: * preferred therapy Abbreviations: CNS – central nervous system; HIV = human immunodeficiency virus; IV - intravenous		

IDSA – Practice Guidelines for the Diagnosis and Management of Aspergillosis

A 2016 guideline on the treatment of aspergillosis was performed by the Infectious Disease Society of America (IDSA).[5] The quality of evidence was graded from low to high and recommendations were issued a "weak" or "strong" designation. There were some conflicts of interest between the IDSA authors and industry; however, the chair was free of conflicts, there is a detailed description of how conflicts are managed and transparent guideline methodology is outlined on the IDSA website. This policy applies to all the IDSA guidelines discussed in this review.

Recommendations for treatment (**Table 3**) and prophylaxis (**Table 4**) for aspergillosis are described below. Duration of treatment is indication dependent. Secondary prophylaxis is recommended for patients who have been treated for aspergillosis who require additional immunosuppression to prevent recurrence. In cases where salvage therapy is indicated, it is recommended to change the antifungal, taper or reverse the immunosuppressant if feasible, and resect any necrotic lesions. Combination antifungal therapy from different classes may be indicated for use as salvage therapy (weak recommendation; moderate-quality of

evidence). Antifungals used in salvage therapy include the following: lipid formulation of amphotericin B, micafungin, caspofungin, posaconazole or itraconazole (strong recommendation; moderate-quality of evidence).

Table 3. IDSA Treatment Recommendations for Aspergillosis[5]

Therapy	Recommendation	Strength of Recommendation	Quality of Evidence
General Treatment Recommendations			
Amphotericin B deoxycholate and lipid derivatives	Initial and salvage therapy when voriconazole is not an option	Strong	moderate
Aerosolized formulations of Amphotericin B	Prophylaxis in patients with prolonged neutropenia	Weak	low
Echinocandins	Salvage therapy alone or in combination, not as primary monotherapy	Strong	moderate
Triazoles	Preferred for treatment and prevention of invasive aspergillosis	Strong	high
	Therapeutic drug monitoring is recommended for patients on prolonged therapy with anticipated drug interactions taking itraconazole, voriconazole, and posaconazole suspension	Strong	moderate
	Trough drug concentration should be obtained for itraconazole, voriconazole, posaconazole and possibly isavuconazole for maximum efficacy and avoidance of toxicities	Strong	moderate
Invasive Pulmonary Aspergillosis (IPA)			
Voriconazole	Recommended as primary treatment for IPA	Strong	high
Liposomal amphotericin B and isavuconazole	Recommended alternative treatments for IPA	Strong	moderate
Other lipid formulations of amphotericin B	Alternative treatment for IPA	Weak	moderate
Combination therapy with voriconazole and echinocandin	Can be considered in select patients	Weak	moderate
Echinocandins	Not recommended as primary therapy	Strong	moderate
Tracheobronchial Aspergillosis (TBA)			
Mold-active triazole or IV lipid formulations of Amphotericin B	Recommended for invasive forms of TBA	Strong	moderate
Central Nervous System Aspergillosis			
Voriconazole	Recommended as primary therapy	Strong	moderate
Lipid Amphotericin B	Recommended for those intolerant or refractory to voriconazole	Strong	moderate
Extrapulmonary Aspergillosis			
Voriconazole	Recommended for central nervous system aspergillosis, aspergillus osteomyelitis and septic arthritis	Strong	moderate
Lipid formulations of amphotericin B	Recommended for those intolerant or refractory to voriconazole	Strong	moderate

Voriconazole plus intravitreal voriconazole or intravitreal amphotericin B	Recommended for aspergillus endophthalmitis	Strong	low
Voriconazole or lipid formulation of amphotericin B	Recommended for aspergillosis of paranasal sinuses	Strong	moderate
Voriconazole or lipid formulation of amphotericin B	Recommended for initial therapy of aspergillus endocarditis, pericarditis and myocarditis	Strong	low
Voriconazole	Recommended for cutaneous aspergillosis, aspergillus peritonitis, or aspergillus ear infection	Strong	low
Voriconazole	Recommended for esophageal, gastrointestinal and hepatic aspergillosis	Weak	low
Amphotericin B deoxycholate	Recommended for renal aspergillosis	Weak	low
Itraconazole or voriconazole	Recommended for aspergillus bronchitis in non-transplant patients	Weak	low
Allergic Syndromes of Aspergillus			
Itraconazole	Recommended for patients with cystic fibrosis who have frequent exacerbations and/or falling FEV1 and monitoring of drug levels	Weak	low
Pediatric Patients with Aspergillosis diagnosis			
Same as adult patients; however, dosing may be different and majority of pharmacokinetic data and experience has been obtained with voriconazole		Strong	high

Table 4. IDSA Prophylaxis Recommendations for Aspergillosis[5]

Therapy	Recommended Indications	Strength of Recommendation	Level of Evidence
Posaconazole	• prolonged neutropenia with high risk of invasive aspergillosis • allogenic HSCT recipients with GVHD who are at high risk for invasive aspergillosis	Strong	high
Voriconazole	• prolonged neutropenia with high risk of invasive aspergillosis • allogenic HSCT recipients with GVHD who are at high risk for invasive aspergillosis	Strong	moderate
Micafungin	• prolonged neutropenia with high risk of invasive aspergillosis	Weak	low
Caspofungin	• prolonged neutropenia with high risk of invasive aspergillosis	Weak	low
Itraconazole	• prolonged neutropenia with high risk of invasive aspergillosis • allogenic HSCT recipients with GVHD who are at high risk for invasive aspergillosis • may be limited by absorption and tolerance	Strong	moderate
Voriconazole, itraconazole or inhaled amphotericin B	• prophylaxis in patients with lung transplant	Strong	moderate
Lipid formulation of amphotericin B or echinocandin	• prolonged neutropenia who remain febrile despite broad-spectrum antibiotic therapy	Strong	high
Voriconazole	• prolonged neutropenia who remain febrile despite broad-spectrum antibiotic therapy	Strong	moderate
Oral itraconazole and voriconazole	• chronic or saprophytic syndromes of aspergillosis	Strong	high

Posaconazole	• chronic or saprophytic syndromes of aspergillosis as a third-line therapy	Strong	moderate
Abbreviations: GVHD – graft- versus- host disease; HSCT = hematopoietic stem cell transplant			

IDSA – Clinical Practice Guideline for the Treatment of Coccidioidomycosis

An update to the guidance on the treatment of coccidioidomycosis was complete by IDSA in 2016.[6] While coccidioidomycosis is not commonly seen in the Pacific Northwest, cases have been reported. Severity of infection can range from pulmonary infections that resolve without treatment to potentially severe pulmonary and extrapulmonary infections. The guideline rates quality of evidence from low to high and recommendations were issued a "weak" or "strong" designation. Guidance for treatment is outline in **Table 5**.[6] In conclusion, antifungal therapy, especially azole antifungals, are the standard first-line therapy for patients with coccidioidomycosis.

Table 5. IDSA Treatment Recommendations for Coccidioidomycosis[6]

Indication	Recommendation	Strength of Recommendation	Quality of Evidence
Newly diagnosed, uncomplicated coccidioidal pneumonia (non-pregnant adults)	Azole antifungal (e.g., fluconazole greater than or equal to 400 mg)	Strong	low
Symptomatic chronic cavitary coccidioidal pneumonia	Oral fluconazole or itraconazole	Strong	moderate
Rupture coccidioidal cavity	Oral azole therapy or amphotericin B for those you cannot tolerate azoles	Strong	very low
Extrapulmonary soft tissue coccidioidomycosis (not associated with bone)	Azole therapy, fluconazole or itraconazole	Strong	moderate
Bone and/or joint coccidioidomycosis	Azole therapy and amphotericin B for severe osseous disease	Strong	low
Newly diagnosed coccidioidomycosis meningitis	Fluconazole 400-1200 mg daily orally Treatment should be life-long Higher doses of therapy or intrathecal amphotericin B can be given if initial treatment fails	Strong	moderate
Allogenic or autologous hematopoietic or solid organ transplant recipients with active coccidioidomycosis	Fluconazole 400 mg daily or appropriate dose based on renal function	Strong	low
Allogenic or autologous hematopoietic or solid organ transplant recipients with active coccidioidomycosis with very severe and/or rapidly progressing acute pulmonary or disseminated coccidioidomycosis	Amphotericin B followed by fluconazole once patient is stabilized	Strong	low
Recipients of biological response modifiers with active coccidioidomycosis	Oral azole antifungals or amphotericin B if severe	Strong	low
Pregnant women with nonmeningeal coccidioidal infection in first trimester	Intravenous amphotericin B	Strong	moderate
Pregnant women with coccidioidal meningitis	Intrathecal amphotericin B	Strong	moderate

Pregnant women with coccidioidal meningitis after first trimester	Azole antifungal, fluconazole or itraconazole	Strong	low
Infants with suspected coccidioidomycosis	Empiric fluconazole 6-12 mg/kg daily	Strong	low
Patients infected with HIV with clinical evidence of coccidioidomycosis and peripheral blood CD4+ t-lymphocyte count of <250 cells/microliter	Antifungal therapy	Strong	low
Organ transplant recipients without active coccidioidomycosis in endemic areas	Oral azole (e.g., fluconazole 200 mg) for 6-12 months	Strong	low

IDSA – Management of Candidiasis

In 2016, IDSA updated the recommendations for managing candidiasis.[8] This guideline updates the previous guidance of 2009. The guideline rates quality of evidence from very low to high and recommendations were issued a "weak" or "strong" designation. Treatment recommendations with moderate to high level of evidence (unless only low quality evidence is available) are provided in **Table 6**.[8] Duration of therapy is dependent upon the diagnosis. Echinocandins are recommended first-line for most episodes of candidemia and invasive candidiasis with the exception of central nervous system, eye and urinary tract infections. The azole antifungals are also commonly indicated first-line and as step-down therapy for candidiasis.

Table 6. IDSA Treatment Recommendations for Candidiasis[8]

Recommendation	First-line Therapy	Alternate Therapies	Strength of Recommendation	Quality of Evidence
Treatment of candidemia in non-neutropenic patients†	• Echinocandins	• fluconazole • Amphotericin B is an alternative if there is intolerance, limited availability or resistance	Strong	high
		• Transition to from echinocandin fluconazole within 5-7 days	Strong	moderate
		• Transition from amphotericin B to fluconazole is recommended within 5-7 days	Strong	high
Treatment of candidemia in neutropenic patients (including treatment in urinary tract infections)	• Echinocandin therapy as initial therapy	• Lipid formulation of amphotericin B	Strong	moderate
Neonatal disseminated candidiasis	• Amphotericin B deoxycholate	• Fluconazole	Strong	moderate
Treatment of intra-abdominal candidiasis	• Lipid formulation of amphotericin B if there is an intolerance to other antifungals		Strong	moderate
Valve endocarditis candidiasis	• Lipid formulation of amphotericin B (with or without flucytosine) • high dose echinocandins	• Step-down therapy with fluconazole 400-800 mg	Strong	low

Valve endocarditis candidiasis without valve replacement option and prosthetic valve endocarditis	• Fluconazole 400-800 mg daily		Strong	low
Implantable cardiac devices infected with candida	• Fluconazole 400-800 mg daily		Strong	low
Candida suppurative thrombophlebitis	• Lipid formulation of amphotericin B • fluconazole 400-800 mg daily • echinocandins	• Fluconazole step-down therapy 400-800 mg	Strong	low
Candida osteoarticular infections	• Fluconazole 400 mg for 6-12 months • Echinocandin for at least 2 weeks followed by fluconazole 400 mg for 6-12 months		Strong	low
Candida septic arthritis	• Fluconazole 400 mg daily for 6 weeks • Echinocandin for 2 weeks followed by fluconazole 400 mg for at least 4 weeks		Strong	low
Candida *Chorioretinitis* without vitritis	• Fluconazole 800 mg loading dose and then 400-800 mg daily • Voriconazole 400 mg IV twice daily for 2 doses and then 300 mg daily	• Liposomal amphotericin B as an alternative	Strong	low
CNS candidiasis	• Liposomal amphotericin B (with or without flucytosine)	• Step-down therapy with fluconazole 400-800 mg	Strong	low
Prophylaxis for patients undergoing urologic procedures	• Fluconazole 400 mg or amphotericin B deoxycholate for several days before and after procedure		Strong	low
Symptomatic candida cystitis	• Fluconazole 200 mg daily for 2 weeks		Strong	moderate
Symptomatic ascending candida pyelonephritis	• Fluconazole 200-400 mg daily for 2 weeks	• Amphotericin B for fluconazole-resistant organisms	Strong	low
Vulvovaginal candidiasis	• Fluconazole 150 mg single dose for uncomplicated and 2-3 doses for severe infection	• Recurring infection should be treated with 10-14 days of topical therapy or oral fluconazole followed by oral fluconazole 150 mg weekly for 6 months	Strong	high

Oropharyngeal candidiasis	• Clotrimazole troches 10 mg, 5 times daily • Miconazole mucoadhesive buccal 50 mg tablets		Strong	high
		• Nystatin suspension as an alternative	Strong	moderate
		• Fluconazole 100-200 mg once daily for 7-14 days for moderate to severe disease	Strong	high
		• Itraconazole, voriconazole, posaconazole or amphotericin B deoxycholate for fluconazole refractory disease	Strong	moderate
		• Echinocandin or amphotericin B deoxycholate for refractory disease	Weak	moderate
		• Fluconazole 100 mg three times weekly for recurrent infections	Strong	high
Esophageal candidiasis	• Fluconazole 200-400 mg for 14-21 days	• Itraconazole or voriconazole • IV fluconazole or echinocandins if oral therapy not tolerated • Echinocandin for refractory disease • Fluconazole 100-200 mg three times a week for recurrent esophagitis	Strong	high
		• Amphotericin deoxycholate if oral therapy not tolerated	Strong	moderate
Key: † Voriconazole is effective for candidemia but does not offer an advantage over fluconazole therapy Abbreviations: CNS- central nervous system; IV – intravenous;				

NCCN – Prevention and Treatment of Cancer-Related Infections, Version 2.2016, NCCN Clinical Practice Guideline

The National Comprehensive Cancer Network (NCCN) 2016 updated guidance on treating cancer-related infections focused on antiviral and antifungal prophylaxis.[7] Literature was systematically reviewed and recommendations were graded based on **Table 7.** Recommendations as they pertain to antifungal treatment will be presented. Patients at intermediate to high risk of infection should be considered candidates for prophylaxis during neutropenia and for anticipated mucositis (**Table 8).**[7] Limitations to the guidance include lack of high-quality evidence available for over half of the recommendations.

Table 7. National Comprehensive Cancer Network Categories of Evidence and Consensus[7]

Category	Description
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate

Table 8. National Comprehensive Cancer Network Recommendations for Antifungal Therapy in Patients with Cancer-related Infections[7]

Disease/Therapy Examples	Antifungal Prophylaxis	Duration	Evidence Grade
Intermediate to High Infection Risk			
ALL	Fluconazole or Micafungin Amphotericin B	Until resolution of neutropenia	Category 2B
MDS (neutropenic) AML (neutropenic)	Posaconazole	Until resolution of neutropenia	Category 1
	Voriconazole, Fluconazole, Micafungin, or Amphotericin B products	Until resolution of neutropenia	Category 2B
Autologous HCT with mucositis	Fluconazole or Micafungin	Until resolution of neutropenia	Category 1
Autologous HCT without mucositis	Consider no prophylaxis	Until resolution of neutropenia	Category 2B
Allogeneic HCT (neutropenic)	Fluconazole or Micafungin	Continue during neutropenia and for at least 75 d after transplant	Category 1
	Voriconazole, Posaconazole, or Amphotericin B products	Continue during neutropenia and for at least 75 d after transplant	Category 2B
Significant GVHD	Posaconazole	Until resolution of significant GVHD	Category 1
	Voriconazole, Echinocandin, Amphotericin B products	Until resolution of significant GVHD	Category 2B
KEY: ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, MDS = myelodysplastic syndromes, GVHD = graft-versus-host disease, HCT = hematopoietic cell transplant			

After review, six guidelines were excluded due to poor quality.[5,6,10,13–15]

New Indications:

Naftifine 1% and 2% cream (Naftin): In 2016, the FDA approved the use of naftifine in pediatric patients 12 and older with interdigital tinea pedis and tinea cruris and age 2 and above with tinea coporis.[16]

Luliconazole 1% cream (Luzu™): An expanded indication was approved by the FDA in 2018 for the use pediatrics ages 2 to under 18 years with tinea corporis.[17] Approval was based on a double-blind, vehicle controlled, multi-center, randomized controlled trial of 75 pediatric patients with a diagnosis of tinea corporis. Clinical cure rates with luliconazole were experienced in 36 patients (71%) compared to 5 (36%) of patients using vehicle cream.[17]

Voriconazole (Vfend®): An expanded indication to include patients 2 years and older was approved in 2019 by the FDA.[18] The expanded indication was based on two prospective, open-label, non-comparative, multicenter clinical studies in 53 pediatric patients ages 2 years old to 18 years old who received intravenous voriconazole with an option to switch to oral therapy after day 7 in the first study and after day 5 in the second study. The first study included pediatric patients (n=14 available for mITT analysis) with invasive aspergillosis which demonstrated a successful global response at 6 weeks, defined as a resolution or improvement in clinical signs and symptoms and at least 50% resolution of radiological lesions, in 9 (64%) patients receiving voriconazole. The second study included pediatric patients (n=10 available for mITT analysis) with invasive candidiasis including candidemia and esophageal candidiasis requiring primary or salvage therapy.[18] Success was obtained in 7 (70%) of patients taking voriconazole.[18]

New FDA Safety Alerts:

Table 9. 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)
Itraconazole[19]	Sporanox®	10/2017	Precautions	Increased risk of drug interactions due to the ability of itraconazole to inhibit breast cancer resistance protein (BCRP) in addition to already known metabolic pathways
Itraconazole[19]	Sporanox®	05/2018	Precautions	With use of itraconazole in immunocompromised patients (e.g., neutropenia, AIDS or organ transplant patients), the oral bioavailability may be reduced and dose may be to adjusted based on clinical response
Econazole Nitrate[20]	Spectazole	06/2018	Warnings and Precautions	May increase anticoagulant effect; monitoring International Normalized Ratio (INR) is recommended
Terbinafine[21]	Lamisil	01/2019	Warnings and Precautions	Thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome
Ketoconazole[22]	Nizoral	05/2019	Safety Communication	FDA warning to limit prescribing of ketoconazole for skin and nail infections due to the risk of serious liver damage, adrenal gland problems and harmful interactions with other medication.

Randomized Controlled Trials:

A total of 166 citations were manually reviewed from the initial literature search. After further review, 165 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining trial is summarized in the table below. The full abstract is included in **Appendix 2**.

Table 10. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Maertens, et al[3] Phase 3, NI, MC, DB, CG, RCT	Isavuconazole 372 mg (prodrug equivalent to 200 mg isavuconazole)* Vs. Voriconazole† * Given IV three times daily on days one and two and then daily orally or IV thereafter † 6 mg/kg IV twice daily on day 1, 4 mg/kg IV twice daily on day 2, then IV 4 mg/kg twice daily or orally 200 mg twice daily from day 3 onward	Patients with suspected invasive mold disease n=527	All-cause mortality from first dose of study drug till day 42	Isavuconazole: 48 (19%) Voriconazole: 52 (20%) Adjusted TD: -1% (95% CI, -7.8 to 5.7) *Isavuconazole was noninferior to voriconazole (NI margin was set at 10%)*

Abbreviations: CG = comparative group; DB= double-blind; IV = intravenous; MC = multi-center; NI = non-inferiority; PC = placebo-controlled; PG = parallel group; RCT = randomized clinical trial; TD = treatment difference

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Appendix 1: Current Preferred Drug List

Antifungals, Oral

Generic	Brand	Form	Route	PDL
clotrimazole	CLOTRIMAZOLE	TROCHE	MUCOUS MEM	Y
fluconazole	DIFLUCAN	SUSP RECON	ORAL	Y
fluconazole	FLUCONAZOLE	SUSP RECON	ORAL	Y
fluconazole	DIFLUCAN	TABLET	ORAL	Y
fluconazole	FLUCONAZOLE	TABLET	ORAL	Y
nystatin	MYCOSTATIN	ORAL SUSP	ORAL	Y
nystatin	NYSTATIN	ORAL SUSP	ORAL	Y
nystatin	NYSTATIN	TABLET	ORAL	Y
flucytosine	ANCOBON	CAPSULE	ORAL	N
flucytosine	FLUCYTOSINE	CAPSULE	ORAL	N
griseofulvin ultramicrosize	GRISEOFULVIN ULTRAMICROSIZE	TABLET	ORAL	N
griseofulvin ultramicrosize	GRIS-PEG	TABLET	ORAL	N
griseofulvin, microsize	GRISEOFULVIN	ORAL SUSP	ORAL	N
griseofulvin, microsize	GRISEOFULVIN	TABLET	ORAL	N
isavuconazonium sulfate	CRESEMBA	CAPSULE	ORAL	N
itraconazole	TOLSURA	CAP SD DSP	ORAL	N
itraconazole	ITRACONAZOLE	CAPSULE	ORAL	N
itraconazole	SPORANOX	CAPSULE	ORAL	N
itraconazole	ITRACONAZOLE	SOLUTION	ORAL	N
itraconazole	SPORANOX	SOLUTION	ORAL	N
itraconazole	ONMEL	TABLET	ORAL	N
ketoconazole	KETOCONAZOLE	TABLET	ORAL	N
miconazole	ORAVIG	MA BUC TAB	BUCCAL	N
nystatin	NYSTATIN	POWDER	ORAL	N
nystatin	NYSTATIN	POWDER(EA)	ORAL	N
posaconazole	NOXAFIL	ORAL SUSP	ORAL	N
posaconazole	NOXAFIL	TABLET DR	ORAL	N
terbinafine HCl	TERBINAFINE HCL	TABLET	ORAL	N
voriconazole	VFEND	SUSP RECON	ORAL	N
voriconazole	VORICONAZOLE	SUSP RECON	ORAL	N
voriconazole	VFEND	TABLET	ORAL	N
voriconazole	VORICONAZOLE	TABLET	ORAL	N

Antifungals, Topical

Generic	Brand	Form	PDL
miconazole nitrate	ANTIFUNGAL CREAM	CREAM (G)	Y
miconazole nitrate	INZO ANTIFUNGAL	CREAM (G)	Y
miconazole nitrate	MICONAZOLE NITRATE	CREAM (G)	Y
nystatin	NYSTATIN	CREAM (G)	Y
nystatin	NYSTATIN	OINT. (G)	Y
acetic ac/resorcino/salicyl ac	ANTIFUNGAL NAIL	TINCTURE	N
butenafine HCl	BUTENAFINE HCL	CREAM (G)	N
butenafine HCl	MENTAX	CREAM (G)	N
ciclopirox	CICLOPIROX	GEL (GRAM)	N
ciclopirox	CICLOPIROX	SHAMPOO	N
ciclopirox	LOPROX	SHAMPOO	N
ciclopirox	CICLODAN	SOLUTION	N
ciclopirox	CICLOPIROX	SOLUTION	N
ciclopirox	PENLAC	SOLUTION	N
ciclopirox olamine	CICLODAN	CREAM (G)	N
ciclopirox olamine	CICLOPIROX	CREAM (G)	N
ciclopirox olamine	LOPROX	CREAM (G)	N
ciclopirox olamine	CICLOPIROX	SUSPENSION	N
ciclopirox olamine	LOPROX	SUSPENSION	N
ciclopirox/skin cleanser no.28	CICLODAN	COMBO. PKG	N
ciclopirox/skin cleanser no.40	LOPROX	COMBO. PKG	N
ciclopirox/skin cleanser no.40	LOPROX	KIT SS-CLN	N
ciclopirox/urea/camph/men/euc	CICLODAN	SOLUTION	N
ciclopirox/urea/camph/men/euc	CICLOPIROX	SOLUTION	N
clotrimazole	ANTIFUNGAL	CREAM (G)	N
clotrimazole	CLOTRIMAZOLE	CREAM (G)	N
clotrimazole	DESENEX	CREAM (G)	N
clotrimazole	FUNGOID	CREAM (G)	N
clotrimazole	LOTRIMIN AF	CREAM (G)	N
clotrimazole	ALEVAZOL	OINT. (G)	N
clotrimazole	CLOTRIMAZOLE	SOLUTION	N
clotrimazole	FUNGOID	SOLUTION	N
clotrimazole/betameth dip/zinc	DERMACINRX THERAZOLE PAK	COMBO. PKG	N
clotrimazole/betamethasone dip	CLOTRIMAZOLE-BETAMETHASONE	CREAM (G)	N
clotrimazole/betamethasone dip	LOTRISONE	CREAM (G)	N
clotrimazole/betamethasone dip	CLOTRIMAZOLE-BETAMETHASONE	LOTION	N
econazole nitrate	ECONAZOLE NITRATE	CREAM (G)	N
econazole nitrate	ECOZA	FOAM	N

efinaconazole	JUBLIA	SOL W/APPL	N
ketoconazole	KETOCONAZOLE	CREAM (G)	N
ketoconazole	EXTINA	FOAM	N
ketoconazole	KETOCONAZOLE	FOAM	N
ketoconazole	KETOCONAZOLE	SHAMPOO	N
ketoconazole	NIZORAL	SHAMPOO	N
luliconazole	LULICONAZOLE	CREAM (G)	N
luliconazole	LUZU	CREAM (G)	N
miconazole nitrate	ATHLETE'S FOOT SPRAY	AERO POWD	N
miconazole nitrate	REMEDY ANTIFUNGAL	CREAM(ML)	N
miconazole nitrate	FUNGOID TINCTURE	KIT	N
miconazole nitrate	ALOE VESTA	OINT. (G)	N
miconazole nitrate	REMEDY PHYTOPLEX ANTIFUNGAL	OINT. (G)	N
miconazole nitrate	ALOE VESTA	OINT.(ML)	N
miconazole nitrate	ANTIFUNGAL POWDER	POWDER	N
miconazole nitrate	DESENEX	POWDER	N
miconazole nitrate	MICONAZORB AF	POWDER	N
miconazole nitrate	REMEDY PHYTOPLEX ANTIFUNGAL	POWDER	N
miconazole nitrate	ZEASORB	POWDER	N
miconazole nitrate	ZEASORB AF	POWDER	N
miconazole nitrate	FUNGOID TINCTURE	TINCTURE	N
miconazole nitrate/zinc ox/pet	MICONAZOLE-ZINC OXIDE-PETROLTM	OINT. (G)	N
miconazole nitrate/zinc ox/pet	VUSION	OINT. (G)	N
naftifine HCl	NAFTIFINE HCL	CREAM (G)	N
naftifine HCl	NAFTIN	CREAM (G)	N
naftifine HCl	NAFTIFINE HCL	GEL (GRAM)	N
naftifine HCl	NAFTIN	GEL (GRAM)	N
nystatin	NYAMYC	POWDER	N
nystatin	NYATA	POWDER	N
nystatin	NYSTATIN	POWDER	N
nystatin	NYSTOP	POWDER	N
nystatin/emollient combo no.54	PEDIADERM AF	CREAM (G)	N
nystatin/emollient combo no.88	NYATA	CMB GEL PD	N
nystatin/triamcin	MYCONEL	CREAM (G)	N
nystatin/triamcin	MYTREX	CREAM (G)	N
nystatin/triamcin	N.T.A.	CREAM (G)	N
nystatin/triamcin	NYSTATIN W/TRIAMCINOLONE	CREAM (G)	N
nystatin/triamcin	NYSTATIN-TRIAMCINOLONE	CREAM (G)	N
nystatin/triamcin	MYTREX	OINT. (G)	N
nystatin/triamcin	N.T.A.	OINT. (G)	N

nystatin/triamcin	NYSTATIN-TRIAMCINOLONE	OINT. (G)	N
oxiconazole nitrate	OXICONAZOLE NITRATE	CREAM (G)	N
oxiconazole nitrate	OXISTAT	CREAM (G)	N
oxiconazole nitrate	OXISTAT	LOTION	N
sertaconazole nitrate	ERTACZO	CREAM (G)	N
sulconazole nitrate	EXELDERM	CREAM (G)	N
sulconazole nitrate	EXELDERM	SOLUTION	N
tavaborole	KERYDIN	SOL W/APPL	N
terbinafine	LAMISIL AT	GEL (GRAM)	N
terbinafine HCl	ATHLETE'S FOOT	CREAM (G)	N
terbinafine HCl	ATHLETE'S FOOT AF	CREAM (G)	N
terbinafine HCl	LAMISIL AT	CREAM (G)	N
terbinafine HCl	TERBINAFINE	CREAM (G)	N
terbinafine HCl	LAMISIL	SPRAY	N
tolnaftate	ATHLETE'S FOOT	AERO POWD	N
tolnaftate	JOCK ITCH	AERO POWD	N
tolnaftate	LAMISIL AF	AERO POWD	N
tolnaftate	TOLNAFTATE	AERO POWD	N
tolnaftate	ANTIFUNGAL CREAM	CREAM (G)	N
tolnaftate	FUNGOID-D	CREAM (G)	N
tolnaftate	TOLNAFTATE	CREAM (G)	N
tolnaftate	ANTI-FUNGAL	POWDER	N
tolnaftate	LAMISIL AF	POWDER	N
tolnaftate	TOLNAFTATE	POWDER	N
tolnaftate	ATHLETE'S FOOT	SPRAY	N
undecylenic ac/zinc undecylena	ANTIFUNGAL CREAM	CREAM (G)	N
undecylenic ac/zinc undecylena	UNDEX-25	OINT. (G)	N
gentian violet	GENTIAN VIOLET	SOLUTION	
gentian violet/brgreen/proflav	TRIPLE DYE	MED. SWAB	
gentian violet/brilliant green	TRIPLE DYE	LIQUID	

Appendix 2: Abstracts of Comparative Clinical Trials

Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial.

Maertens JA, Raad II, Marr KA, Patterson TF, Kontoyiannis DP, Cornely OA, Bow EJ, Rahav G, Neofytos D, Aoun M, Baddley JW, Giladi M, Heinz WJ, Herbrecht R, Hope W, Karthaus M, Lee DG, Lortholary O, Morrison VA, Oren I, Selleslag D, Shoham S, Thompson GR 3rd, Lee M, Maher RM, Schmitt-Hoffmann AH, Zeiher B, Ullmann AJ.

BACKGROUND:
Isavuconazole is a novel triazole with broad-spectrum antifungal activity. The SECURE trial assessed efficacy and safety of isavuconazole versus voriconazole in patients with invasive mould disease.
METHODS:
This was a phase 3, double-blind, global multicentre, comparative-group study. Patients with suspected invasive mould disease were randomised in a 1:1 ratio using an interactive voice-web response system, stratified by geographical region, allogeneic haemopoietic stem cell transplantation, and active malignant disease at baseline, to receive isavuconazonium sulfate 372 mg (prodrug; equivalent to 200 mg isavuconazole; intravenously three times a day on days 1 and 2, then either intravenously or orally once daily) or voriconazole (6 mg/kg intravenously twice daily on day 1, 4 mg/kg intravenously twice daily on day 2, then intravenously 4 mg/kg twice daily or orally 200 mg twice daily from day 3 onwards). We tested non-inferiority of the primary efficacy endpoint of all-cause mortality from first dose of study drug to day 42 in patients who received at least one dose of the study drug (intention-to-treat [ITT] population) using a 10% non-inferiority margin. Safety was assessed in patients who received the first dose of study drug. This study is registered with ClinicalTrials.gov, number NCT00412893.
FINDINGS:
527 adult patients were randomly assigned (258 received study medication per group) between March 7, 2007, and March 28, 2013. All-cause mortality from first dose of study drug to day 42 for the ITT population was 19% with isavuconazole (48 patients) and 20% with voriconazole (52 patients), with an adjusted treatment difference of -1·0% (95% CI -7·8 to 5·7). Because the upper bound of the 95% CI (5·7%) did not exceed 10%, non-inferiority was shown. Most patients (247 [96%] receiving isavuconazole and 255 [98%] receiving voriconazole) had treatment-emergent adverse events (p=0·122); the most common were gastrointestinal disorders (174 [68%] vs 180 [69%]) and infections and infestations (152 [59%] vs 158 [61%]). Proportions of patients with treatment-emergent adverse events by system organ class were similar overall. However, isavuconazole-treated patients had a lower frequency of hepatobiliary disorders (23 [9%] vs 42 [16%]; p=0·016), eye disorders (39 [15%] vs 69 [27%]; p=0·002), and skin or subcutaneous tissue disorders (86 [33%] vs 110 [42%]; p=0·037). Drug-related adverse events were reported in 109 (42%) patients receiving isavuconazole and 155 (60%) receiving voriconazole (p<0·001).
INTERPRETATION:
Isavuconazole was non-inferior to voriconazole for the primary treatment of suspected invasive mould disease. Isavuconazole was well tolerated compared with voriconazole, with fewer study-drug-related adverse events. Our results support the use of isavuconazole for the primary treatment of patients with invasive mould disease.

Appendix 3: Medline Search Strategy

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

Search Strategy:

#	Searches	Results
1	clotrimazole.mp. or Clotrimazole/	2714
2	fluconazole.mp. or Fluconazole/	11797
3	nystatin.mp. or Nystatin/	4873
4	flucytosine.mp. or Flucytosine/	3473
5	griseofulvin.mp. or Griseofulvin/	3690
6	isavuconazonium.mp.	40
7	itraconazole.mp. or Itraconazole/	8840
8	ketoconazole.mp. or Ketoconazole/	8523
9	miconazole.mp. or Miconazole/	3048
10	posaconazole.mp.	2108
11	terbinafine.mp. or Terbinafine/	2482
12	voriconazole.mp. or Voriconazole/	5368
13	acetic acid.mp. or Acetic Acid/	37476
14	butenafine.mp.	83
15	ciclopirox.mp. or Ciclopirox/	524
16	econazole.mp. or Econazole/	924
17	efinaconazole.mp.	115
18	luliconazole.mp.	68
19	naftifine.mp.	186
20	oxiconazole.mp.	107
21	sertaconazole.mp.	112

22	sulconazole.mp.	81
23	tavaborole.mp.	78
24	tolnaftate.mp. or Tolnaftate/	255
25	gentian violet.mp. or Gentian Violet/	2579
26	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	83394
27	limit 26 to (english language and humans and yr="2015 -Current")	5752
28	limit 27 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	166

Appendix 4: Key Inclusion Criteria

Population	Patients with a fungal infection diagnosis
Intervention	Topical or oral antifungal treatment
Comparator	Other antifungal agents, placebo, or matched controls
Outcomes	Clinical cure, mycological cure, resolution of symptoms or all-cause mortality
Timing	At onset of infection
Setting	Outpatient and inpatient

Antifungals

Goal(s):

- Approve use of antifungals only for OHP-funded diagnoses. Minor fungal infections of skin, nails and scalp, such as dermatophytosis and candidiasis, are only funded when complicated by an immunocompromised host.

Length of Authorization:

- See criteria

Requires PA:

- Non-preferred drugs

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at [17]
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1: Examples of FUNDED indications (1/1/15)

ICD-10	Description
B373	Candidiasis of vulva and vagina
B371	Candidiasis of the lung
B377	Disseminated Candidiasis
B375-376, B3781-3782, B3784-3789	Candidiasis of other specified sites
B380-B384, B3889, B389	Coccidioidomycosis various sites
B392-395, B399, G02, H32, I32, I39, J17	Histoplasmosis
B409,B410, B419, B480	Blastomycosis
B420-427, B429, B439, B449-450, B457, B459, B469, B481-482, B488, B49	Rhinosporidosis, Sporotrichosis, Chromoblastomycosis, Aspergillosis, Mycotis Mycetomas, Cryptococcosis, Allescheriosis, Zygomycosis, Dematiacious Fungal Infection, Mycoses Nec and Nos
B488	Mycosis, Opportunistic
B4481	Bronchopulmonary Aspergillus, Allergic
N739-751, N759, N760-N771(except N72)	Inflammatory disease of cervix vagina and vulva

L3019,L3029, L3039, L3049	Cellulitis and abscess of finger and toe
P375	Neonatal Candida infection

Table 2: Examples of NON-FUNDED indications (1/1/15)

ICD-10	Description
L2083, L210-211, L218-219, L303	Erythematosquamous dermatosis
L22	Diaper or napkin rash
L20.0-20.82, L20.84-20.89	Other atopic dermatitis and related conditions
L240-242, L251-255, L578, L579, L230, L2381, L2481, L250, L252, L258-259, L551-552 , L568, L589	Contact dermatitis and other eczema
L530-532, L510, L518-519, L52, L710-711, L718, L930, L932, L490-L499, L26, L304, L538, L920, L951, L982, L539	Erythematous conditions
L438,L441-443, L449,L661	Lichen Planus
L700-702, L708	Rosacea or acne
B351	Tinea unguium (onychomycosis)
B360	Pityriasis versicolor
B362	Tinea blanca
B363	Black piedra
B368, B369	Mycoses, superficial
B372	Cutaneous candidiasis
B379	Candidiasis, unspecified
R21	Rash and other nonspecific skin eruption

Table 3: Criteria driven diagnoses (1/1/15)

ICD-10	Description
B350	Dermatophytosis of scalp and beard (tinea capitis/ tinea barbae)
B352	Dermatophytosis of hand (tinea manuum)
B356	Dermatophytosis of groin and perianal area (tinea cruris)
B353	Dermatophytosis of foot (tinea pedis)
B355	Dermatophytosis of body (tinea corporis / tinea imbricate)
B358	Deep seated dermatophytosis
B358-B359	Dermatophytosis of other specified sites - unspecified site

B361	Tinea nigra
B370,B3783	Candidiasis of mouth
B3742,B3749	Candidiasis of other urogenital sites

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the diagnosis funded by OHP? (See examples in Table 1).	**Yes:** Go to #3	**No:** Go to #4
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety.	**Yes:** Inform prescriber of preferred alternatives.	**No:** Approve for 3 months or course of treatment.
4. Is the prescriber a hematology, oncology or infectious disease specialty prescriber requesting voriconazole?	**Yes:** Approve for 3 months or course of treatment.	**No:** Go to #5
5. Is the diagnosis not funded by OHP? (see examples in Table 2).	**Yes:** Pass to RPh. Deny; not funded by OHP	**No:** Go to #6
6. Is the diagnosis funded by OHP if criteria are met? (see examples in Table 3).	**Yes:** Go to #7	**No:** Go to #9
7. Is the patient immunocompromised (examples below)? • Does the patient have a current (not history of) diagnosis of cancer **AND** is currently undergoing	**Yes:** Record ICD-10 code. Approve as follows: (immunocompromised patient)	**No:** Go to #8

<table>
<tr>
<td>Chemotherapy or Radiation? Document therapy and length of treatment. OR
• Does the patient have a diagnosis of HIV/AIDS? OR
• Does the patient have sickle cell anemia?
• Poor nutrition, elderly or chronically ill?
• Other conditions as determined and documented by a RPh.</td>
<td>ORAL & TOPICAL
• Course of treatment.
• If length of therapy is unknown, approve for 3 months.</td>
<td></td>
</tr>
<tr>
<td>8. Is the patient currently taking an immunosuppressive drug? Document drug.

Pass to RPh for evaluation if drug not in list.

Immunosuppressive drugs include but are not limited to:
<table>
<tr><td>azathioprine</td><td>leflunomide</td></tr>
<tr><td>basiliximab</td><td>mercaptopurine</td></tr>
<tr><td>cyclophosphamide</td><td>methotrexate</td></tr>
<tr><td>cyclosporine</td><td>mycophenolate</td></tr>
<tr><td>etanercept</td><td>rituximab</td></tr>
<tr><td>everolimus</td><td>sirolimus</td></tr>
<tr><td>hydroxychloroquine</td><td>tacrolimus</td></tr>
<tr><td>infliximab</td><td></td></tr>
</table>
</td>
<td>Yes: Approve as follows: (immunocompromised patient)

ORAL & TOPICAL
• Course of treatment.
• If length of therapy is unknown, approve for 3 months.</td>
<td>No: Pass to RPh. Deny; not funded by the OHP</td>
</tr>
</table>

9. RPh only: All other indications need to be evaluated to see if it is an OHP-funded diagnosis:

- If funded: may approve for treatment course with PRN renewals. If length of therapy is unknown, approve for 3-month intervals only.
- If not funded: Deny; not funded by the OHP.
    - Deny non-fungal diagnosis (medical appropriateness)
    - Deny fungal ICD-10 codes that do not appear on the OHP list pending a more specific diagnosis code (not funded by the OHP).
    - Forward any fungal ICD-10 codes not found in the Tables 1, 2, or 3 to the Lead Pharmacist. These codes will be forwarded to DMAP to be added to the Tables for future requests.

P&T Review: *11/19 (KS) 7/15 (kk); 09/10; 2/06; 11/05; 9/05; 5/05*
Implemented: *5/1/16; 8/15; 1/1/11; 7/1/06; 11/1/0; 9/1/0*

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Drug Class Update: Anticoagulants, Oral and Subcutaneous

Date of Review: November 2019

Date of Last Review: November 2017 – Class Scan
July 2017 – Betrixaban NDE
Date of Literature Search: September 2019

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

Purpose for Class Update:
The purpose of the anticoagulant class update is to review any new comparative effectiveness literature that has been published since the last review and to ensure the preferred drug list (PDL) aligns with current evidence.

Research Questions:
1. Is there new high-quality comparative evidence on the effectiveness of anticoagulants when used for stroke prophylaxis in atrial fibrillation or prophylaxis or treatment of venous thromboembolism (VTE)?
2. Is there new high-quality comparative evidence on the harms of anticoagulants when used for stroke prophylaxis in atrial fibrillation or prophylaxis or treatment of (VTE)?
3. Is there evidence regarding subgroups of patients based on demographics (age, racial groups, gender), socioeconomic status, other medications (drug-drug interactions), comorbidities (drug-disease interactions), or pregnancy for which one anticoagulant is more effective or associated with fewer harms than another anticoagulant?

Conclusions:
- There are thirteen systematic reviews, one guideline and eight randomized controlled trials (RCTs) that provided high-quality evidence for the anticoagulant drug class update.

<u>Venous Thromboembolism</u>
- A high quality systematic review found that prophylaxis with anticoagulants, compared to placebo, after major orthopedic surgery reduces the incidence of deep vein thrombosis (DVT) based on high strength of evidence.[1] In patients with total hip replacement (THR), low-molecular weight heparin (LWMH) was associated with less major bleeding compared to factor Xa inhibitors (FXaIs) (ARR 0.5%) based on moderate quality evidence. Factor Xa inhibitors were associated with a 3% reduction in total DVTs compared to LMWH, 3.4% versus 6.4%, respectively. In patients undergoing THR, DTIs were associated with less risk of total DVT compared to LMWH based on moderate evidence (OR range of 1.14 to 1.52) .[1] Moderate evidence demonstrated a reduction in total DVT events with FXaI when compared to LMWH in patients undergoing TKR, 1.2% versus 2.5%.[1]

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- There is moderate strength of evidence that LMWH has a lower risk of mortality compared to unfractionated heparin (UFH) when used as initial treatment for VTE in patients with cancer, followed by oral therapy for 3 months (57 fewer deaths per 1000 patients treated versus 168 deaths per 1000 patients).[2]
- Moderate strength of evidence found no difference in 3 months of LMWH compared to vitamin K antagonists (VKA) for the treatment of VTE for the outcomes of recurrent VTE and mortality.[3]

Stroke Prophylaxis in Atrial Fibrillation

- A high-quality systematic review and meta-analysis evaluated the use of anticoagulants for the prevention of thromboembolism in patients with atrial fibrillation (AF). Warfarin and rivaroxaban were similarly effective for the outcomes of stroke or systemic embolism. Apixaban was found to be more effective than warfarin (HR 0.79; 95% CI, 0.66 to 0.95) (absolute risk reduction was not provided). Edoxaban was also found to more effective than warfarin for hemorrhagic strokes (HR 0.33; 95% CI, 0.22 to 0.50) but not for overall stroke risk. Dabigatran 150 mg demonstrated superiority over warfarin for stroke and systemic embolism (RR 0.66; 95% CI, 0.53 to 0.82). Major bleeding rates were similar between the direct acting oral anticoagulants (DOACs) and warfarin, with the exception of edoxaban and apixaban which were associated with less major bleeding.[4]
- In patients with chronic kidney disease (CKD) and AF, the efficacy of DOACs was similar to warfarin for the outcome of stroke and systemic embolism prevention based on moderate evidence.[5]
- A high-quality review found risk of stroke and systemic embolism to be less in patients with AF who are treated with FXaIs compared to patients treated with warfarin based on high quality of evidence (odds ration [OR] 0.89; 95% CI, 0.82 to 0.97). Actual differences in event rates between FXaIs and warfarin are small, 34 versus 32 events per 1000 patients.[6]
- There is insufficient direct comparative evidence for comparisons of the DOACs in patients with AF or VTE.

Recommendations:

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

Summary of Prior Reviews and Current Policy

- There is insufficient comparative evidence to universally recommend one anticoagulant over another. There is extensive clinical experience using warfarin; however, DOACs have been shown to have a reduced risk of bleeding in some instances. Clinically efficacy comparisons between warfarin and DOACs have demonstrated similar or superior effectiveness with DOAC therapy, dependent on the indication and outcome studied.
- The last review done in May 2017 resulted in no changes to the PDL. A class update in 2015 resulted in removal of the prior authorization (PA) requirement for most DOACs due to concerns of potentially delaying treatment by requiring prior authorization (PA). Betrixaban still requires a PA, as it is indicated for only hospitalized adult patients.
- An internal drug utilization review in 2017 found that the DOACs were being used appropriately within the Oregon Health Authority (OHA) fee-for-service population.
- A majority of the anticoagulants are available without prior authorization. Drugs requiring a PA include: betrixaban, dalteparin vials, fondaparinux and branded enoxaparin. The anticoagulation class results in a fair amount of expenditures to the OHA with over half the utilization due to DOACs.

Background:
Anticoagulants are used for many indications, most commonly VTE or stroke treatment and prophylaxis. In the last year, the number of patients in the fee-for-service population with an indication for anticoagulation (e.g., stroke, AF, DVT, PE, or VTE) was approximately 400. One to two patients per 1000 people are affected by DVT/pulmonary embolism (PE) annually and approximately 100,000 patients die each year from VTE.[7] The United States (US) prevalence of stroke is approximately 800,000 new and secondary strokes a year.[8] An additional new indication for anticoagulants is the use for reduction in risk of major cardiovascular events (CV death, MI and stroke) when used in combination with aspirin for patients with chronic coronary artery disease (CAD) or peripheral artery disease (PAD). Low-dose rivaroxaban (2.5 mg twice daily) is the first DOAC to be approved for this indication; however, evidence suggests a marginal clinical benefit with an actual risk reduction (ARR) of 1.3% in favor of rivaroxaban 2.5 mg twice daily + aspirin compared to aspirin + placebo, 4.1% versus 5.4% (**Table 7**).[9]

The pathophysiology of thrombosis results from damage to the endothelial lining of blood vessels which trigger activation of the coagulation cascade leading to thrombus formation.[10] Anticoagulant pharmacotherapy targets aspects of the clotting cascade to exhibit a therapeutic effect. Injectable anticoagulants work by enhancing antithrombin (AT) which is responsible for inhibiting a variety of clotting factors. Oral anticoagulants exhibit anticoagulant activity through blocking the formation of vitamin K clotting factors (warfarin), direct thrombin inhibition (dabigatran) or factor Xa inhibition (apixaban, edoxaban, and rivaroxaban).[10]

Anticoagulants recommended for VTE are: warfarin, LMWH, and DOACs.[11] Some guidelines preference the use of DOACs over warfarin for VTE disease.[11] For patients with VTE and cancer, the use of LMWH is recommended over other anticoagulants.[11] However, there is accumulating data supporting DOACs in this patient population. For patients undergoing THR or TKR, prophylactic anticoagulants are considered standard practice. Low-molecular weight heparins and DOACs are most commonly used for THR or TKR; however, warfarin is a viable alternative.[1] Patients with AF are at increased risk of stroke and systemic embolism. Anticoagulation is recommended for patients with an elevated CHA_2DS_2-VASc score (2 or greater in men and 3 or greater in women) by some guidance and advocated for patients at lower risk by alternate guidelines.[12,13] Warfarin has been traditionally used first-line for stroke prophylaxis; however, recent guidance recommends DOACs as preferred therapy. Evidence has demonstrated equivalent or superior efficacy of DOACs to warfarin with similar or reduced risk of major bleeding.[13]

The most important outcomes in assessing therapy for treatment and prevention of VTE include the occurrence or reoccurrence of VTE and all-cause mortality. Additional relevant outcomes include: major and minor bleeding, cardiovascular events and withdrawals due to adverse events. Early research relied primarily on symptomatic VTE and fatal PE as measures of antithrombotic prophylaxis efficacy. Recent trials evaluating the anticoagulant efficacy in patients undergoing hip or knee replacement often use the surrogate outcome, asymptomatic DVT, detected by mandatory venography.[36] Many studies that rely on asymptomatic DVT events to determine treatment differences and are not powered to detect a difference in the frequency of symptomatic events, due to low occurrence rates, which is the more clinically relevant outcome.[37] This limitation should be considered when interpreting findings from trials studying the use of anticoagulants in patients undergoing TKR or THR.

Rates of stroke, systemic embolisms and mortality are appropriate outcomes in evaluating treatment for AF. Secondary outcomes of interest are rates of ischemic and hemorrhagic strokes and incidence of myocardial infarctions (MI). Important safety outcomes include major bleeds, clinically relevant non-major bleeds and gastrointestinal bleeding.

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

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

New Systematic Reviews:

Venous Thromboembolism

AHRQ – Venous Thromboembolism Prophylaxis in Major Orthopedic Surgery
A 2017 review from the Agency for Healthcare Research and Quality (AHRQ) analyzed literature published from January 2010 thru June 2016, which updated the 2012 review.[1] A total of 142 studies were included, 127 of which were randomized controlled trials (RCTs). High risk of bias related to maintaining blinding was found in 52 of the studies, 28 had high risk of bias in maintaining intention-to-treat (ITT) methodology, 8 had high risk of bias for data analysis and 22 had high risk of bias related to attrition bias. Fifty-four percent of the trials were funded by industry.[1] Fifteen non-randomized comparative studies were also included. The following classes of drugs were included: antiplatelet drugs (aspirin), direct thrombin inhibitors (dabigatran and desirudin), FEI (TB402 – not approved in the US), Factor XaI (apixaban, darexaban, edoxaban, eribaxaban, fondaparinux, rivaroxaban and TAK422), Factor Ii (Factor XI antisense oligonucleotide), LMWH (dalteparin, enoxaparin, semuloparin, tinzaparin), mechanical devices, unfractionated heparin, and VKAs (warfarin).[1] Findings for therapies Food and Drug Administration (FDA) approved in the United States (U.S.) on outcomes with moderate to high strength of evidence will be discussed. Evidence for within-class comparisons of thromboprophylaxis was insufficient to draw conclusions.

Total Hip Replacement
Direct thrombin inhibitors were found to prevent more DVTs than LMWH based on moderate evidence; however, LMWHs were associated with less major bleeding (**Table 1**).[1] Evidence for the comparison of LMWH to FXaI found less major bleeding with LMWH but efficacy findings were inconsistent. LMWHs were associated with a reduction in VTEs and major bleeding compared to UFH. Comparisons of LMWH and aspirin found similar risk of VTE outcomes and major bleeding between both groups. Patients treated with lower doses of LMWH were found to have less bleeding compared patients treated with higher doses of LMWH based on moderate strength of evidence. Treatment with LMWH two weeks or longer was more effective in reducing total DVT and proximal DVT compared to shorter durations (up to 10 days or to hospital discharge).[1]

Table 1. Outcome Results for Total Hip Replacement for Anticoagulant Class Comparisons[1]

Comparison	Outcome	Results (Summary OR Range of OR Estimates)*	Strength of Evidence
LMWH vs. DTI	DVT, total	Range: 1.14 to 1.52 *Favors DTI*	Moderate
	DVT, proximal	Range: 1.35 to 1.89 *Favors DTI*	Moderate
LMWH vs. FXaI	DVT, total	LMWH: 6.4% FXaI: 3.4% 1.71 (95% CI, 1.22 to 2.39) *Favors FXaI*	Moderate
	DVT, proximal	LMWH: 1.8% FXaI: 0.74% 2.40 (95% CI, 1.23 to 4.69) *Favors FXaI*	Moderate
	Major bleeding	LMWH: 1.2% FXaI: 1.7% 0.74 (95% CI, 0.54 to 0.99) *LMWH is associated with less bleeding*	High
	Serious adverse events	0.95 (95% CI, 0.78 to 1.17) *No difference between treatments*	Moderate
LMWH vs. UFH	PE, total	LMWH: 0.85% UFH: 2.9% 0.29 (95% CI, 0.13 to 0.63) *Favors LMWH*	High
	DVT, total	LMWH: 14.4% UFH: 16.3% 0.84 (95% 0.60 to 1.18) *No difference between treatments*	Moderate
	DVT, proximal	LMWH: 4.9% UFH: 7.9% 0.59 (95% CI, 0.38 to 0.93) *Favors LMWH*	Moderate
	Major bleeding	LMWH: 2.1% UFH: 4.6% 0.46 (95% CI, 0.23 to 0.92)`	Moderate

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		LMWH is associated with more bleeding	
LMWH vs. VKA	Major bleeding	LMWH: 1.5% VKA: 0.75% 1.96 (95% CI, 1.14 to 3.38) *VKA is associated with more bleeding*	High
Mechanical devices vs. VKA	DVT, proximal	Range: 2.39 to 4.69 *Favors VKA*	High
LMWH low dose (enoxaparin 20 or 30 mg) vs. high dose (enoxaparin 40 mg)	Major bleeding	LMWH low: 1.6% LMWH high: 5% 0.42 (95% CI, 0.21 to 0.86) *LMWH low dose is associated with less bleeding*	Moderate
LMWH short duration (usually less than 28 days) vs. long duration (usually longer than 28 days)	DVT, proximal	LMWH short: 13% LMWH long: 4.5% 2.94 (95% CI, 1.62 to 5.35) *Favors LMWH long*	Moderate

Key: * ARRs presented when available
Abbreviations: DTI – direct thrombin inhibitor; DVT – deep vein thrombosis; FXaI – factor Xa inhibitor; LMWH – low molecular weight heparin; OR – odds ratio; PE – pulmonary embolism; UFH – unfractionated heparin; VKA – vitamin K antagonist

Total Knee Replacement

Evidence for the use of anticoagulants in patients undergoing TKR are presented in **Table 2**. There was a lower incidence of VTE when treated with FXaI compared to LMWH. Low molecular weight heparin was found to result in a lower incidence of DVT compared to VKAs in patients undergoing TKR.[1] There was high strength of evidence that patients who received higher doses of the DTI, dabigatran 220 to 225 mg (not currently available), had a reduced risk of total DVT and moderate evidence of less proximal DVT than lower doses (i.e., dabigatran 150 mg).[1] Total VTE was reduced in patients taking higher doses of DTIs compared to lower doses based on moderate evidence.

Table 2. Outcome Results for Total Knee Replacement for Anticoagulant Class Comparisons[1]

Comparison	Outcome	Results (Summary OR Range of Estimates)*	Strength of Evidence
LMWH vs. FXaI	DVT, proximal	LMWH: 2.5% FXaI: 1.2% 1.84 (95% CI, 1.07 to 3.16) *Favors FXaI*	Moderate
LMWH vs. VKA	DVT, total	Range: 0.42 to 0.67 *Favors LMWH*	High

DTI low dose (dabigatran 150 mg vs. high dose (dabigatran 220 mg)	DVT, total	Range: 1.54 to 2.08 *Favors high dose*	High
	DVT, proximal	1.57 (95% CI, 0.83 to 2.96) *Favors high dose*	Moderate
FXaI low vs. high dose (twice the lower dose)	VTE, total	FXaI low: 23% FXaI high: 13% 2.06 (95% CI, 1.48 to 2.86) *Favors high dose*	Moderate

Key: * ARRs presented when available
Abbreviations: DVT – deep vein thrombosis; FXaI – factor Xa inhibitor; LMWH – low molecular weight heparin; VKA – vitamin K antagonist

Hip Fracture Surgery

Only six trials were available for analysis and evidence was insufficient for most outcomes. There was moderate evidence that the risk of total DVT was lower with LMWH compared to FXaI.[1]

Findings of this systematic review are limited by total number of DVTs as an outcome for 82% of the included studies, which includes symptomatic and asymptomatic DVTs. Asymptomatic DVTs are not commonly identified in non-study populations, and therefore, the clinically applicability to PE and other vascular outcomes is unknown. Additionally, symptomatic DVTs and other clinically relevant outcomes were only reported in one-third and two-thirds of studies, respectively. The low incidence of PE makes it difficult to determine a correlation with DVT incidence. There was also evidence of selective outcome reporting which has the potential to result in inconsistent conclusions.

Cochrane – Vitamin K antagonists versus Low-molecular-weight Heparin for the Long-term Treatment of Symptomatic Venous Thromboembolism

Symptomatic venous thromboembolism that requires long-term (3 months) therapy with VKAs or LMWH was evaluated by a 2017 Cochrane review.[3] Sixteen trials (n=3299) met criteria for inclusion. Type of VTE was separated into: PE (3 trials), symptomatic DVT and symptomatic PE (1 trial), and symptomatic DVT (12 trials). Seven of the sixteen trials were considered to be of high methodological quality. There was a high risk of performance bias for all included studies and a high risk of allocation bias in a majority of studies. Other domains of bias were low or unclear.

Recurrent VTE rates were similar between LMWH and VKA based on moderate evidence (OR 0.83; 95% CI, 0.60 to 1.15; P=0.27).[3] Moderate quality evidence found no difference in mortality rates between LMWH and VKA with follow-up ranging up to 9 months (OR 1.08; 95% CI, 0.75 to 1.56; P =0.68).[3] There were no differences in bleeding rates between the two therapies. There was imprecision for the outcome of major bleeding preventing strong conclusions favoring either treatment.

There are limitations to the evidence, such as low number of events resulting in imprecision in the data. Different initial treatment of VTE may have also influenced the results. Lack of blinding due to administration differences and settings of administration (inpatient vs. outpatient) introduced a high degree of performance bias. Overall, there are no efficacy and safety differences in using LMWH versus VKA for long-term VTE treatment.

Cochrane – Low Molecular Weight Heparin for Prevention of Venous Thromboembolism in Patients with Lower-Limb Immobilization

A 2017 Cochrane review assessed the effectiveness of LWMH for VTE prevention in ambulatory patients with lower-limb immobilization.[14] LMWH (tinzaparin and dalteparin) use was compared to placebo or no prophylaxis in 8 trials. Risk of bias was low for allocation and blinding. Incomplete outcome data and selective reporting had a high risk of bias in 3 trials. Primary efficacy outcomes were DVT, PE and mortality.

There was moderate evidence of a reduction in DVT in patients receiving LMWH compared to placebo, 87 per 1000 patients versus 174 per 1000 patients (OR 0.45; 95% CI, 0.33 to 0.61) in patients who were receiving therapy during period of immobilization.[14] Findings for all other outcomes were based on low quality evidence and therefore no strong conclusions were able to be drawn. Minor bleeding was rare and not substantially different between groups.

Stroke

AHRQ – Stroke Prevention in Patients with Atrial Fibrillation

A 2018 review done by AHRQ evaluated the comparative effectiveness of vitamin K antagonists (warfarin), DOACs (apixaban, dabigatran, edoxaban and rivaroxaban) and procedural interventions for stroke prevention in patients with AF.[4] This report updates the review from 2013 with the addition of 122 studies. A total of 117 studies contributed to the evidence for prophylactic anticoagulation use. Seventy-five studies were found to be good-quality with a low risk of bias. Bleeding risk and predictive utility of VTE clinical imaging was also investigated.

There was moderate strength of evidence that CHADS2, CHA2DS2-VASc, Framingham score, and Age, Biomarkers (cTnI-hs and NT-proBNP) and Clinical history (ABC) score provide limited prediction of stroke events (moderate strength of evidence).[4] Assessment of predictive factors for bleeding found the HAS-BLED assessment to be effective for predicting major bleeding events in patients taking warfarin for AF based on moderate strength of evidence. Moderate strength of evidence found patients with chronic kidney disease to be at increased risk of bleeding.

Evidence for the use of anticoagulants for the prevention of stroke in patients with nonvalvular AF are presented in **Table 3**.[4] For the majority of therapies superior efficacy is associated with increased risk of bleeding. Warfarin has consistently shown to be more effective than aspirin for stroke prevention and combination therapy of clopidogrel + aspirin is more effective than aspirin alone, for those patients who are not candidates for warfarin or DOACs.[4] Dabigatran 150 mg has been shown to be more effective than warfarin for the outcome of stroke and systemic embolism reduction and associated with similar rates of major bleeding. Mortality benefit and MI risk has been inconsistent in comparisons between dabigatran and warfarin.[4] Apixaban has been shown to be superior to aspirin and superior to warfarin for the outcomes of stroke and systemic embolism with similar or reduced incidence of bleeding. All-cause mortality was also shown to be decreased with apixaban compared to warfarin but this was based on low strength of evidence. Rivaroxaban and warfarin are associated with similar efficacy and major bleeding rates. Edoxaban has demonstrated a lower hemorrhagic stroke risk compared to warfarin but similar overall stroke risk with similar rates of major bleeding.

Limitations to the findings include the lack of direct head-to-head comparisons of the DOACs and high risk of publication bias associated with a majority of included studies being manufacturer funded.

Table 3. Anticoagulants for Thromboembolic Prevention in Patients with Nonvalvular AF[4]ǂ

Comparison	Outcome	Results	Strength of Evidence/Notes
Aspirin Vs. Warfarin	Ischemic Stroke	No pooled results *Warfarin superior to aspirin*	Moderate
	Bleeding	No pooled results *Warfarin was associated with more bleeding than aspirin*	Moderate
Warfarin + aspirin Vs. Aspirin	Ischemic stroke	HR 1.27 (95% CI, 1.14 to 1.40) *Increased risk with warfarin + aspirin*	Moderate
	Bleeding	No pooled results *Increased risk with warfarin + aspirin*	Moderate
Clopidogrel + aspirin Vs. Aspirin	Any stroke	HR 0.72 (96% CI, 0.62 to 0.83) *Clopidogrel + aspirin superior to aspirin*	Moderate
	Hemorrhagic stroke	No pooled results *Similar risk between treatments*	Moderate
	Systemic embolism	HR 0.96 (95% CI, 0.66 to 1.40) *Similar risk between therapies*	Moderate
	Major bleeding	HR 1.57 (95% CI, 1.29 to 1.92) *Increased bleeding risk with clopidogrel + aspirin*	Moderate
	Minor bleeding	HR 2.42 (95% CI, 2.03 to 2.89) *Increased bleeding risk with clopidogrel + aspirin*	Moderate
	All-cause mortality	HR 0.98 (95% CI, 0.89 to 1.08) and HR 1.12 (95% CI, 0.65 to 1.90) *Similar risks between treatments*	Moderate Results not pooled
Clopidogrel Vs. Warfarin	Ischemic stroke	*HR 1.86 (95% CI, 1.52 to 2.27)* *Increased risk compared to warfarin*	Moderate
	Bleeding	*HR 1.06 (95% CI, 0.87 to 1.29)* *Similar risk between therapies*	Moderate
Clopidogrel + aspirin Vs. Warfarin	Stroke or systemic embolism	HR 1.56 (95% CI, 1.17 to 2.10) and HR 1.72 (95% CI, 1.24 to 2.37) *Increased risk with clopidogrel + aspirin*	High Results not pooled
	Hemorrhagic stroke	HR 0.34 (95% CI, 0.12 to 0.93) *Increased risk with warfarin*	Moderate
	Major bleeding	HR 1.10 (95% CI, 0.83 to 1.45) *Similar rates between groups*	Moderate
	Minor bleeding	HR 1.23 (95% CI, 1.09 to 1.39) *Increased risk with clopidogrel + aspirin*	Moderate

	All-cause mortality	HR 1.01 (95% CI, 0.81 to 1.26) *Similar risk between therapies*	Moderate
	Death from vascular causes	HR 1.14 (95% CI, 0.88 to 1.48) *Similar risk between therapies*	Moderate
	Myocardial infarction	No pooled results *Similar risk between therapies*	Moderate
Warfarin + clopidogrel Vs. Warfarin	Bleeding	HR 3.08 (95% CI, 2.32 to 3.91) *Increased risk with warfarin + clopidogrel*	Moderate
Warfarin Vs. Warfarin + aspirin + clopidogrel	Bleeding	HR 3.07 (95% CI, 2.89 to 4.76) *Increased risk with triple therapy*	Moderate
Dabigatran 150 mg Vs. Warfarin	Hemorrhagic	RR 0.26 (95% CI, 0.14 to 0.49)* *Dabigatran superior to warfarin*	High
	Stroke or systemic embolism	RR 0.66 (95% CI, 0.53 to 0.82)* *Dabigatran superior to warfarin*	High
	Major bleeding	RR 0.93 (95% CI, 0.81 to 1.07)* *Dabigatran superior to warfarin*	High
	Minor bleeding	RR 0.91 (95% CI, 0.85 to 0.97)* *Dabigatran superior to warfarin*	Moderate
	Intracranial bleeding	RR 0.40 (95% CI, 0.27 to 0.60)* *Dabigatran superior to warfarin*	High
	Death from vascular causes	RR 0.85 (95% CI, 0.72 to 0.99) *Dabigatran superior to warfarin*	Moderate
	Hospitalizations	RR 0.97 (95% CI, 0.92 to 1.03)* *No difference between treatments*	Moderate
	Adverse events (dyspepsia)	Dabigatran: 11.3% Warfarin: 5.8% P<0.001 *Dyspepsia more common with dabigatran*	Moderate
Dabigatran 110 mg Vs. Warfarin	Stroke or systemic embolism	RR 0.91 (95% CI, 0.74 to 1.11)* *No difference between treatments*	Moderate
	Ischemic or uncertain stroke	RR 1.11 (95% CI, 0.89 to 1.40)* *No difference between treatments*	High
	Hemorrhagic stroke	RR 0.31 (95% CI, 0.17 to 0.56)* *Dabigatran superior to warfarin*	High

	Major bleeding	RR 0.80 (95% CI, 0.69 to 0.93)* *Dabigatran superior to warfarin*	High
	Minor bleeding	RR 0.79 (95% CI, 0.74 to 0.84) *Dabigatran superior to warfarin*	Moderate
	Intracranial bleeding	RR 0.31 (95% CI, 0.20 to 0.47)* *Dabigatran superior to warfarin*	High
	Death from vascular causes	RR 0.90 (95% CI, 0.77 to 1.06) *No difference between treatments*	Moderate
	Hospitalizations	RR 0.92 (95% CI, 0.87 to 0.97)* *Dabigatran reduced risk of hospitalizations*	High
	Adverse events (dyspepsia)	Dabigatran: 11.8% Warfarin: 5.8% P<0.001 *Dyspepsia more common with dabigatran*	Moderate
Factor Xa inhibitors (apixaban, edoxaban, rivaroxaban) Vs. Warfarin	Stroke or systemic embolism	HR 0.92 (95% CI, 0.71 to 1.17) *No difference between treatments*	Moderate There was high strength of evidence demonstrating superiority of apixaban to warfarin when analyzed separately
	Ischemic or uncertain stroke	HR 1.06 (95% CI, 0.77 to 1.46) *No difference between treatments*	Moderate to high
	Hemorrhagic stroke	HR 0.48 (95% CI, 0.32 to 0.72) *Factor Xa superior to warfarin*	Low to high
	Systemic embolism	HR 0.87 (95% CI, 0.44 to 1.75) *No difference between treatments*	Moderate for apixaban Moderate for rivaroxaban Moderate for edoxaban
	Major bleeding	HR 0.72 (95% CI, 0.43 to 1.22) *No difference between treatments*	Low to high Apixaban superior to warfarin and rivaroxaban inferior to warfarin*
	Intracranial bleeding	HR 0.45 (95% CI, 0.28 to 0.75) *Factor Xa superior to warfarin*	Moderate to high
	Gastrointestinal bleeding	HR 0.94 (95% CI, 0.78 to 1.12) *No difference between groups*	Low rivaroxaban inferior to warfarin*
	All-cause mortality	HR 0.90 (95% CI, 0.86 to 0.94) *Factor Xa superior to warfarin*	Low to moderate
	Death from CV causes	HR 0.87 (95% CI, 0.84 to 0.90)	Moderate

		Factor Xa superior to warfarin	
	MI	HR 0.96 (95% CI, 0.73 to 1.25) *No difference between treatments*	Moderate to high
	Adverse events	*No difference between treatments*	Moderate for apixaban
	Medication adherence	*Better adherence with rivaroxaban*	Moderate for rivaroxaban
Factor Xa Vs. Dabigatran	Major bleeding	HR 0.91 (95% CI, 0.66 to 1.24) *No difference between treatments*	Apixaban and rivaroxaban superior to dabigatran* Apixaban superior to rivaroxaban*
	Gastrointestinal bleeding	HR 0.84 (95% CI, 0.47 to 1.49) *No difference between treatments*	
Apixaban Vs. Aspirin	Stroke or systemic embolism	HR 0.45 (95% CI, 0.32 to 0.62) *Apixaban superior to aspirin*	Moderate
	Ischemic	HR 0.37 (95% CI, 0.25 to 0.55) *Apixaban superior to aspirin*	Moderate
	Hemorrhagic stroke	HR 0.67 (95% CI, 0.24 to 1.88) *No difference between treatments*	Moderate
	Major bleeding	HR 1.13 (95% CI, 0.74 to 1.75) *No difference between treatments*	Moderate
	Minor bleeding	HR 1.20 (95% CI, 1.00 to 1.53) *Apixaban increased risk*	Moderate
	Death from vascular causes	HR 0.87 (95% CI, 0.66 to 1.17) *No difference between treatments*	Moderate
	Myocardial infarction	HR 0.86 (95% CI, 0.50 to 1.48) *No difference between treatments*	Moderate
	Hospitalizations	HR 0.79 (95% CI, 0.69 to 0.91) *Apixaban reduced risk*	Moderate
	Adverse events	*No difference between treatments*	Moderate

Key: * observational and RCT data combined ł No absolute risk reductions were reported
Abbreviations: CI – confidence interval; CV – cardiovascular; HR – hazard ratio; MI – myocardial infarction; RR – relative risk

Cochrane – Factor Xa Inhibitors versus Vitamin K Antagonists for Preventing Cerebral or Systemic Embolism in Patients with Atrial Fibrillation

Factor Xa inhibitors were directly compared to warfarin for cerebral or systemic embolism prevention in patients with AF in a 2018 Cochrane review.[6] Thirteen randomized controlled trials lasting more than 4 weeks were eligible for inclusion. Warfarin was compared to apixaban, betrixaban, darexaban (discontinued), edoxaban, and rivaroxaban. Follow-up ranged from 12 weeks to 2.8 years. Risk of bias was generally low for all domains except for blinding. Six trials were double-blinded, six were single-blinded studies and one open-label study was included.[6] The primary endpoint was the composite of all strokes (ischemic and hemorrhagic) and systemic embolic events.

Results are presented in **Table 4**. Factor Xa inhibitors were superior to warfarin for all outcomes studied including; stroke and other systemic embolism, all strokes, major bleeding, intracranial hemorrhage, and all-cause death.[6] Additional considerations are that the actual differences between warfarin and factor Xa inhibitors are small and unlikely to be clinically significant for the primary endpoint, all strokes and all-cause death; however, major bleeding is lower with Factor Xa inhibitors. Additionally, NNT values are high for individual study results for edoxaban, apixaban and rivaroxaban for the outcome of overall reduction in stroke and systemic embolism. Findings for major bleeds were associated with high heterogeneity and therefore conclusions are less robust.

Table 4. Factor Xa and Warfarin Comparisons for Cerebral and Systemic Embolism Prevention in Patients with AF*[6]

Outcome	Results (number per 1000 patients)†	Strength of Evidence/Notes	Conclusion
Stroke and other systemic embolism	Warfarin: 34 per 1000 Factor Xa inhibitors: 32 per 1000 OR 0.89; 95% CI, 0.82 to 0.97	High	Factor Xa inhibitors superior to warfarin - actual difference per 1000 patients treated is small
All strokes	Warfarin: 30 per 1000 Factor Xa inhibitors: 28 per 1000 OR 0.89; 95% CI, 0.81 to 0.97	High	Factor Xa inhibitors superior to warfarin - actual difference per 1000 patients treated is small
Major bleeding	Warfarin: 51 per 1000 Factor Xa inhibitors: 41 per 1000 OR 0.73; 95% CI, 0.73 to 0.84	Moderate	Factor Xa inhibitors superior to warfarin
Intracranial hemorrhage	Warfarin: 13 per 1000 Factor Xa inhibitors: 7 per 1000 OR 0.50; 95% CI, 0.42 to 0.59	High	Factor Xa inhibitors superior to warfarin
All-cause death	Warfarin: 67 per 1000 Factor Xa inhibitors: 66 per 1000 OR 0.89; 95% CI, 0.83 to 0.95	Moderate	Factor Xa inhibitors superior to warfarin – actual difference per 1000 patients treated is small
Key: * Majority of data from apixaban, edoxaban, and rivaroxaban studies, † based on assumed risk (median control group risk across studies) for warfarin and corresponding risk (relative effect) for factor Xa inhibitors Abbreviations: CI = confidence interval; OR = odds ratio;			

Cochrane – Direct Oral Anticoagulants versus Warfarin for Preventing Stroke and Systemic Embolic Events Among Atrial Fibrillation Patients with Chronic Kidney Disease

Cochrane reviewed the evidence for the use of DOACs compared to warfarin in patients with chronic kidney disease (CKD) with AF.[5] Anticoagulants included in the review are: apixaban (2.5 mg or 5 mg – dose adjusted based on SrCr), dabigatran (110 mg or 150 mg), edoxaban (30 mg), rivaroxaban (10 mg or 15 mg) and warfarin. Patients with AF were defined as having CKD by a creatinine clearance (CrCl) or estimated glomerular filtration rate (eGFR) between 15 and 60 mL/min (considered stage G3 or G4 CKD stage). Most of the participants had G3 CKD. Five studies lasting 1.8 to 2.8 years were included in the review. All studies had an unclear risk of bias and a high risk of bias for publication bias.

There is moderate evidence that DOACs decreased the risk of stroke and systemic embolism in patients with CKD to a similar extent as warfarin, 6 less per 1000 patients (RR 0.81; 95% CI, 0.65 to 1.00).[5] Gastrointestinal bleeding was found to be higher with DOACs compared to warfarin with an incidence of 24 per 1000 compared to 17 per 1000 patients (RR 1.40; 95% CI, 0.97 to 2.01) (moderate evidence).[5] There was moderate evidence that warfarin was associated with more risk of intracranial hemorrhage compared to DOACs, 14 versus 6 per 1,000 patients (RR 0.43; 95% CI, 0.27 to 0.69).[5] All-cause mortality was not different between warfarin and DOACs based on moderate evidence (RR 0.91; 95% CI, 0.78 to 1.05).[5]

Limitations to the evidence include the small number of patients with G4 CKD, limiting applicability to this population. In conclusion, the efficacy and safety of DOACs was similar to warfarin in prevention of stroke and systemic embolism in patients with AF who also have CKD.

Cancer

Cochrane – Oral anticoagulation in People with Cancer who Have no Therapeutic or Prophylactic Indication for Anticoagulation

The efficacy and safety of using anticoagulants in ambulatory patients with cancer and otherwise no indication for anticoagulation use was evaluated in a 2017 Cochrane review.[15] Vitamin K antagonists and DOACs were included in the review. Patients eligible for the review were undergoing systemic anticancer therapy and were initiated on anticoagulation within 4 weeks of starting chemotherapy. Anticoagulation was continued during chemotherapy and up to 3 weeks after treatment had ceased. Seven placebo-controlled or no intervention trials were included in the review; 6 warfarin trials and 1 apixaban trial. The risk of bias was low for all domains except for allocation concealment, which was unclear. Primary outcomes of interest were mortality, VTE, symptomatic DVT, PE and bleeding risk.

For the outcome of mortality at 12 months, no clinically meaningful differences were found in the deaths in patients receiving warfarin and those receiving no treatment (RR 0.95; 95% CI, 0.87 to 1.03).[15] There was an increased risk of major and minor bleeding in patients receiving warfarin compared to no prophylaxis, 107 major bleeding events per 1000 patients and 167 minor bleeding events per 1000 patients treated with warfarin ($p<0.05$ for both), respectively (moderate evidence).[15] For the one trial that evaluated apixaban, all outcomes were found to have low strength of evidence and therefore no conclusions of efficacy over no treatment could be made.

Limitations to the evidence include only a small number of trials of short duration. Overall, there was no benefit of warfarin in patients with cancer with no therapeutic or prophylactic indication and anticoagulation was associated with more minor and major bleeding. There was insufficient evidence to make conclusions for the effect of apixaban.

Cochrane – Anticoagulation for the Initial Treatment of Venous Thromboembolism in People with Cancer

A 2018 Cochrane review evaluated the efficacy and safety of anticoagulation therapy in patients with cancer who develop VTE.[2] Therapies included in the review were fixed dosed LMWH, UFH, and fondaparinux. Fifteen studies were included in the review; 13 studies compared LMWH to UFH, one compared fondaparinux to heparin and one compared dalteparin to tinzaparin. Initial parenteral anticoagulation was followed by oral anticoagulation for 3 months in all but one study. Patients were treated as inpatients and outpatients.

The is moderate evidence that after 3 months the use of LMWH, for initial anticoagulation, was associated fewer deaths compared to UFH (57 vs. 168 per 1000 patients 168 deaths per 1000 patients (RR 0.66; 95% CI, 0.40 to 1.10).[2] Recurrent VTE was less frequent with LMWH compared to UFH, 30 vs. 96 per 1000 (RR 0.69; 95% CI, 0.27 to 1.76).[2] Heparin was associated with a mortality benefit over fonadaparinux for initial treatment of VTE in patients with cancer with a RR of 1.25 (95% CI, 0.86 to 1.81).[2] Eight fewer patients taking fondaparinux developed recurrent VTE compared to heparin in which 117 patients per 1000 developed recurrent VTE (moderate evidence). Major bleeding was more common with fondaparinux (RR 0.82; 95% CI, 0.40 to 1.66) compared to more minor bleeding with heparin (RR 1.53; 95% CI, 0.88 to 2.66).[2] Comparison of tinzaparin to dalteparin as initial treatment found no statistically significant differences between groups for relevant efficacy and safety outcomes.

Limitations to the evidence include a high risk of performance bias and publication bias. Direct comparisons to DOACs as initial therapy would also inform decisions on optimal initial therapy in patients with VTE and cancer.

Cochrane – Parenteral Anticoagulation in Ambulatory Patients with Cancer

Ambulatory patients with cancer with no other indication for parenteral anticoagulation beyond cancer treatment were the focus of a 2019 Cochrane review.[16] Nineteen trials were included, all trials evaluated LMWH except one which used unfractionated heparin. Patients who were being treated with chemotherapy, hormonal therapy, immunotherapy, or radiotherapy for a cancer diagnosis were included. All cancer types were eligible for inclusion, most commonly pancreatic cancer, small cell lung cancer, non-small cell lung cancer.[16] The overall risk of bias was low for most studies.

Results at 12 months found no difference in mortality rates between heparin and no therapy, 494 versus 504 per 1000 patients treated (RR 0.98; 95% CI, 0.93 to 1.03), with similar results at 24 months (RR 0.99; 95% CI, 0.96 to 1.01) (moderate evidence).[16] The risk of symptomatic VTE was 38 per 1000 patients given heparin prophylaxis compared to 68 per 1000 in patients not treated with prophylaxis based on high strength of evidence (RR 0.56; 95% CI, 0.47 to 0.68).[16] Major and minor bleeding were higher in patients receiving heparin compared to no prophylaxis based on moderate and high evidence, respectively. There was moderate evidence that patients treated with heparin had a lower risk of thrombocytopenia compared to no prophylaxis; however, results were associated with a high degree of heterogeneity and results were not statistically significant (RR 0.69; 95% CI, 0.37 to 1.27; I^2 = 83%).[16] Quality of life was not different between groups.

Additional evidence directly comparing anticoagulants for prophylaxis in patients with cancer would be helpful. In summary prophylaxis with heparins have to no effect on mortality but reduced the incidence of symptomatic VTE, with an increase in minor and major bleeding, in patients with cancer.

Cochrane – Anticoagulation for Perioperative Thromboprophylaxis in People with Cancer

A 2018 Cochrane review researched the role of anticoagulants (LMWH, UFH, or fondaparinux) for the prevention of mortality, DVT, PE, bleeding and thrombocytopenia in people with cancer undergoing a surgical intervention.[17] Twenty trials were included in the analysis. Trials were at low risk of bias except for the domain of allocation concealment. There was moderate evidence of no difference between LMWH and UFH for outcomes listed in **Table 5.** Comparisons between LMWH and fondaparinux also found no difference between therapies for efficacy and safety outcomes, based on low certainty of evidence. Limitations to the review include the potential for insufficient power to detect a difference between drugs.

Table 5. LMWH Compared to UFH in Patients with Cancer Undergoing Surgery[17]

Outcome*	Results (number per 1000 patients)†	Strength of Evidence/Notes	Conclusion
Mortality	UFH: 51 per 1000 LMWH: 42 per 1000 RR 0.82; 95% CI, 0.63 to 1.07	Moderate	No difference between therapies
Any PE	UFH: 6 per 1000 LMWH: 3 per 1000 RR 0.49; 95% CI, 0.17 to 1.47	Moderate	No difference between therapies
Symptomatic DVT	UFH: 10 per 1000 LMWH: 7 per 1000 RR 0.67; 95% CI, 0.27 to 1.69	Moderate	No difference between therapies
Major bleeding	UFH: 31 per 1000 LMWH: 31 per 1000 RR 1.01; 95% CI, 0.69 to 1.48	Moderate	No difference between therapies
Minor bleeding	UFH: 142 per 1000 LMWH: 143 per 1000 RR 1.01; 95% CI, 0.76 to 1.33	Moderate	No difference between therapies
Wound hematoma	UFH: 86 per 1000 LMWH: 60 per 1000 RR 0.70; 95% CI, 0.54 to 0.92	Moderate	LMWH superior to UFH
Reoperation for bleeding	UFH: 51 per 1000 LMWH: 47 per 1000 RR 0.93; 95% CI, 0.57 to 1.50	Moderate	No difference between therapies
Intraoperative blood loss	MD 6.75 lower in LMWH group	Moderate	No difference between therapies
Postoperative drain volume	MD 30.18 higher with LMWH	Moderate	No difference between therapies
Thrombocytopenia	UFH: 3 per 1000 LMWH: 6 per 1000 RR 3.07; 95% CI, 0.32 to 29.33	Moderate	No difference between therapies

Abbreviations: * Follow-up 1 week to 3 months
Key: CI = confidence interval; DVT = deep-vein thrombosis; LMWH = low-molecular weight heparin; MD = mean difference; PE = pulmonary embolism; RR = relative risk; UFH = unfractionated heparin

Cochrane – Anticoagulation for People with Cancer and Central Venous Catheters

The efficacy and harms of using anticoagulants in people with cancer and central venous catheters (CVC) was reviewed in a 2019 Cochrane report.[18] Anticoagulants in the review included: VKAs, LMWH, UFH and fondaparinux. Seven trials evaluated LMWH compared to no LMWH, six trials compared VKA to no VKA and three trials evaluated LMWH to VKA. Risk for attrition and performance bias was high in all studies. Allocation concealment and reporting bias were unclear for most of the studies.

Moderate evidence found a reduction in the risk of symptomatic catheter-related VTE at 3 months in patients treated with LMWH compared to no treatment, 38 fewer VTE events per 1000 patients (RR 0.43; 95% CI, 0.22 to 0.81).[18] There was only low quality evidence available for mortality and bleeding comparisons. There was no quality evidence to inform benefits or harms of VKA versus no VKA. Comparisons between LMWH and VKA in adults found no conclusive benefits or risks between therapies when used for patients with CVC.

Most of the evidence for this review was considered low or very-low quality, preventing an accurate assessment of comparative efficacy and safety between therapies and use of no therapy. Overall, there seems to be a benefit of using LMWH in preventing catheter-related VTE in patients with cancer, however; risks of bleeding should be weighed against benefit of anticoagulation.

Cochrane – Prolonged Thromboprophylaxis with Low Molecular Weight Heparin for Abdominal or Pelvic Surgery

A 2019 review evaluated LMWH for extended prophylaxis (at least 14 days) compared to LMWH administration during the inpatient period only, after abdominal or pelvic surgery for the outcome of VTE prevention.[19] Seven trials were included in the analysis all comparing LMWH to placebo for prolonged prophylaxis.

There was moderate quality of evidence that all VTE was reduced with prolonged LMWH compared inpatient hospital treatment only, 5.3% versus 13.2% (OR 0.38; 95% CI, 0.26 to 0.54).[19] The incidence of DVT was reduced with prolonged anticoagulation with LMWH compared to no prolonged anticoagulation with an OR of 0.39 (95% CI, 0.27 to 0.55) (moderate evidence).[19] Proximal DVT and symptomatic VTE rates were also decreased with prolonged LMWH use compared to inpatient treatment alone. Symptomatic VTE, which is the most clinically relevant outcome, was found to be decreased by 7 fewer events per 1000 patients in those individuals treated with prolonged LMWH compared to inpatient therapy (OR 0.30; 95% CI, 0.08 to 1.11).[19] Bleeding rates were not statistically or clinically different between prolonged LMWH prophylaxis compared to none, 3.4% versus 2.8% based on moderate quality of evidence. Moderate quality evidence found no difference in mortality rates between in hospital treatment compared to prolonged treatment, 38 and 43 per 1000 patients, respectively.[19]

Limitations include unclear and high risk of bias in many domains and small, short term trials available for data analysis. Evidence suggest prolonged prophylaxis with LMWH is more effective than in-patient only anticoagulation.

After review, thirty 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:

High Quality Guidelines:

NICE – Venous Thromboembolism – Reducing the Risk of Hospital-Acquired Deep Vein Thrombosis or Pulmonary Embolism

A 2018 review by NICE outlined preventative recommendations for VTE and DVT prevention in patients 16 years old and older who are admitted to the hospital.[20] For adults under 18 who require pharmacological VTE prophylaxis, the recommendation is to use apixaban, aspirin, dabigatran, fondaparinux, LMWH or rivaroxaban. Patients whose risk of VTE outweighs their risk of bleeding who take antiplatelet therapies for other conditions should be considered for VTE prophylaxis. Mechanical prophylaxis can be considered if the risk of bleeding outweighs the risk of VTE.

The following patients should be considered for VTE prophylaxis if their risk of VTE outweighs the risk of bleeding:[20]

- Patients who are interrupting anticoagulation therapy and are at increased risk of VTE
- LMWH should be offered first-line for a minimum of seven days to acutely ill medical patients
- Patients with cancer who are receiving cancer modifying treatments should not routinely receive anticoagulation unless they have another indication
- Patients with myeloma who are receiving chemotherapy with thalidomide, pomalidomide or lenalidomide with steroids are candidates for aspirin or LMWH
- Patients with pancreatic cancer who are receiving chemotherapy should get LMWH
- LMWH is recommended first line for patients receiving palliative care (that are not in their last days of life). Fondaparinux is the preferred second-line therapy
- Patients who are admitted into the critical care unit should receive LMWH unless contraindicated
- LMWH is recommended first-line and fondaparinux is recommended second-line for patients admitted to an acute psychiatric ward
- Patients subject to lower limb immobilization, due to orthopedic surgery, are candidate for LMWH or fondaparinux. Consider stopping at day 42 if immobilization continues.
- A month of VTE prophylaxis should be considered in patients with fragility fractures of the pelvis, hip or proximal femur
    - LMWH initiated 6-12 hours post-surgery
    - Fondaparinux initiated 6 hours after surgery if patient is at low risk of bleeding
- Pre-operative VTE prophylaxis should be considered for patients with fragility fractures of the pelvis, hip or proximal femur who has surgery delayed one day beyond the day of admission. LMWH should be discontinued at least 12 hours before surgery and fondaparinux should be stopped at least 24 hours before surgery
- Patients undergoing elective hip replacement surgery should receive VTE prophylaxis:
    - LMWH for 10 days followed by aspirin (75 or 150 mg) for an additional 28 days
    - LMWH for 28 days combined with anti-embolism stockings (until discharge)
    - Rivaroxaban can also be considered an option (evidence of a small efficacy benefit for total DVT of rivaroxaban over the other DOACs when compared to LMWH)
    - Apixaban and dabigatran may be an option if contradictions to the options above
- Options for patients undergoing elective knee replacement include: (any of the following are recommended in no specific order)
    - Aspirin (75 or 150 mg) for 14 days
    - LMWH for 14 days with anti-embolism stockings (until discharge)
    - Rivaroxaban

- Apixaban and dabigatran may be an option if contradictions to the options above

Additional Guidelines for Clinical Context:

ACC/AHA/HRS Guideline on Management of Patients with Atrial Fibrillation

The 2014 American College of Cardiology (ACC), American Heart Association (AHA) and Heart Rhythm Society (HRS) guidelines on management of patients with atrial fibrillation were updated in 2019.[13] Due to lack of details on guideline methodology and a significant portion of the professional practice committee members having conflicts of interest with industry, and the associations themselves funded partially by industry the guideline will not be reviewed in detail or relied upon for policy making decisions.

AHS Guideline for the Management of Venous Thromboembolism Prophylaxis

In 2018 the American Society of Hematology (ASH) provided guideline recommendations for the prophylaxis of VTE in hospitalized and nonhospitalized patients.[21] Many guideline panel members have conflicts of interest with industry and the AHS is heavily funded by pharmaceutical companies. For these reasons the guidelines will not be discussed in detail or relied upon for making policy decisions.

CHEST – Antithrombotic Therapy for Atrial Fibrillation

The 2018 guidelines for the management of patients with atrial fibrillation was published by the American College of Chest Physicians.[12] The chair of the guidelines has multiple ties with industry and only three of the twelve panel members were free from conflicts of interest. Additionally, CHEST obtains industry support which could bias clinical recommendations. Therefore, guideline recommendations will not be presented or relied on for policy decisions.

After review, four guidelines were excluded due to poor quality (e.g., lack of details on methodology, authors with extensive conflicts of interest with industry).[22–25]

New Formulations or Indications:

Indications:

Rivaroxaban (Xarelto®): The FDA approved expanding the indication for rivaroxaban to include the use for reduction in risk of major cardiovascular events (CV death, MI and stroke) when used in combination with aspirin for patients with chronic CAD or PAD (**Table 7**). [9,26]

Rivaroxaban (Xarelto®): In October 2019, rivaroxaban was approved for the prophylaxis of VTE in acutely ill medical patients at risk for thromboembolic complications not at high risk of bleeding.[9] Approval was based on a 2013 study which demonstrated a reduction at day 35 in the composite primary endpoint (asymptomatic proximal DVT in lower extremity, symptomatic proximal or distal DVT in the lower extremity, symptomatic non-fatal PE and death related to VTE) with rivaroxaban 10 mg daily for 35 ± 4 days compared with enoxaparin 40 mg once daily for 10 ± 4 days (followed by placebo), 4.4% versus 5.7% (RR 0.77; 95% CI, 0.62 to 0.96).[9] As with other indications, the dose of rivaroxaban should be decreased in patients with reduced creatinine clearance (less than 30 mL/min) and discontinuation of therapy should be considered in patients who develop acute renal failure.[9]

Dalteparin (Fragmin®): Dalteparin received approval for the treatment of symptomatic VTE to reduce the recurrence in pediatric patients 1 month of age and older.[27]

New FDA Safety Alerts:

Table 6. 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)
Betrixaban[28]	Bevyxxa®	1/2019	Warnings	Reduce the dose for patients on p-glycoprotein inhibitors and avoid concomitant use with p-glycoprotein inducers. Avoid use in patients with moderate or severe hepatic impairment. Store between 59 and 86 degrees Fahrenheit.
Enoxaparin[29]	Lovenox	10/2017	Contraindications	History of immune-mediated heparin-induced thrombocytopenia (HIT) within the past 100 days or in the presence of circulating antibodies
Rivaroxaban[9]	Xarelto®	10/2018	Warnings and Precautions	Increased risk of thrombosis in patients with antiphospholipid syndrome: use is not recommended

Randomized Controlled Trials:

A total of 236 citations were manually reviewed from the initial literature search. After further review, 228 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 8 trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 7. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Anderson, et al[30] MC, DB, RCT, Phase 3	Rivaroxaban 10 mg Vs. Aspirin 81 mg All patients received initial rivaroxaban 10 mg till postoperative day 5 Patients were followed for 90 days	Patients undergoing hip or knee arthroplasty N= 3424	Occurrence of symptomatic venous thromboembolism	Rivaroxaban: 12 (0.70%) Aspirin: 11 (0.64%) MD 0.06%; 95% CI, -0.55 to 0.66 P<0.001 for noninferiority and P=0.84 for superiority *Rivaroxaban and aspirin demonstrated similar efficacy*
Calkins, et al[31]	Dabigatran 150 mg twice daily Vs.	Patients scheduled for a catheter ablation	Incidence of major bleeding during and up to 8 weeks after ablation	Dabigatran: 5 (1.6%) Warfarin: 22 (6.9%) MD -5.3%; 95% CI, -8.4 to -2.2

RCT, OL, MC, Phase 4	Warfarin (INR target 2.0 - 3.0) Treatment duration: 12-16 weeks	of paroxysmal or persistent atrial fibrillation N = 704		P<0.001 *Dabigatran was associated with less bleeding compared to warfarin*
Diener, et al[32] MC, DB, RCT, Phase 3	Dabigatran 150 mg or 110 mg twice daily Vs. Aspirin 100 mg daily Median follow-up: 19 months	Patients who had embolic stroke of undetermined source N=5390	Recurrent stroke	Dabigatran: 177 (6.6%) Aspirin: 207 (7.7%) HR 0.85; 95% CI, 0.69 to 1.03 P=0.10 *There was no difference in efficacy between dabigatran and aspirin in stroke prevention*
Eikelboom, et al[26] (COMPASS) MC, DB, DD, RCT, Phase 3	Rivaroxaban 2.5 mg twice daily + aspirin 100 mg daily Vs. Rivaroxaban 5 mg twice daily + placebo Vs. Aspirin 100 mg daily + placebo Mean follow-up: 23 months	Patients with stable vascular disease N=27,395	Composite of cardiovascular death, myocardial infarction or stroke	Rivaroxaban 2.5 mg + aspirin: 4.1% Rivaroxaban 5 mg + placebo: 4.9% Aspirin + placebo: 5.4% Rivaroxaban 2.5 mg + aspirin vs. aspirin: HR 0.76 (95% CI, 0.66 to 0.86) P < 0.001 *Rivaroxaban 2.5 mg + aspirin superior to aspirin alone* Rivaroxaban 5.0 mg vs. aspirin: HR 0.90 (95% CI, 0.79 to 1.03) P = 0.12 *Rivaroxaban 5.0 mg not superior to aspirin alone*
Goette, et al [33] (ENSURE-AF) MC, OL, RCT, Phase 3	Edoxaban 60 mg daily Vs. Enoxaparin - warfarin‡ Follow-up: up to 12 months	Patients with stable vascular disease N=2,199	Composite of stroke, systemic embolic event, myocardial infarction and cardiovascular mortality	Edoxaban: 5 (<1%) Enoxaparin - warfarin: 11 (1%) OR 0.46 (95% CI, 0.12 to 1.43) *Edoxaban had similar efficacy to enoxaparin - warfarin*
Hart, et al[34]	Rivaroxaban 15 mg daily + placebo	Patients with recent ischemic	First recurrence of ischemic or hemorrhagic stroke or systemic	Rivaroxaban + placebo: 172 (5.1%) Aspirin + placebo: 160 (4.8%)

MC, DB, DD, RCT, Phase 3	Vs. Aspirin 100 mg daily + placebo Median follow-up: 11 months	stroke that was presumed to be from a cerebral embolism but without arterial stenosis, lacune or an identified cardioembolic sources N=7,213	embolism in a time-to-event analysis	HR 1.07 (95% CI, 0.87 to 1.33) P = 0.52 *Rivaroxaban was not superior to aspirin and associated with more bleeding (trial was terminated early)*
Lopes, et al[35] RCT, Phase 4, OL* and DB†	Apixaban Vs. Vitamin K antagonist And Aspirin Vs. Placebo Treatment duration: 6 months	Patients with AF and an acute coronary syndrome or undergone PCI and were planning on taking a P2Y12 inhibitor N= 4,614	Major of clinically relevant nonmajor bleeding	Apixaban: 10.5% Vitamin K antagonist: 14.7% HR 0.69; 95% CI, 0.58 to 0.81 P<0.001 *Apixaban caused less bleeding than vitamin K antagonists* Aspirin: 16.1% Placebo: 9.0% HR 1.89; 95% CI, 1.59 to 2.24 P<0.001 *Aspirin was associated with more bleeding than placebo*
Weitz, et al[36] (EINSTEIN CHOICE) MC, DB, RCT, Phase 3	Rivaroxaban 10 mg daily Vs. Rivaroxaban 20 mg daily Vs. Aspirin 100 mg daily Mean follow-up: approximately 1 year	Patients with VTE and previous 6-12 months of anticoagulation therapy who were equipoise regarding the need for continued anticoagulation N=3,396	Symptomatic or recurrent fatal or nonfatal VTE	Rivaroxaban 20 mg: 17 (1.5%) Rivaroxaban 10 mg: 13 (1.2%) Aspirin: 50 (4.4%) Rivaroxaban 20 mg vs. Aspirin HR 0.34 (95% CI, 0.20 to 0.59) P<0.001 *Rivaroxaban 20 mg was more effective than aspirin* Rivaroxaban 10 mg vs. Aspirin HR 0.26 (95% CI, 0.14 to 0.47) P<0.001 *Rivaroxaban 10 mg was more effective than aspirin*

Key: * Apixaban versus warfarin was open-label † Aspirin versus placebo was double-blind (patients received 2 or 3 active treatments dependent upon randomization) ‡ Patients in enoxaparin – warfarin group were started on both and stayed only on warfarin once INR was ≥2
Abbreviations: AF = atrial fibrillation; CAD = coronary artery disease; DB = double-blind; DD = double-dummy; HR = hazard ratio; INR = international normalized ratio; MC = multi-center; OL = open-label; RCT = randomized clinical trial; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; VTE = venous thromboembolism

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
apixaban	ELIQUIS	TAB DS PK	ORAL	Y
apixaban	ELIQUIS	TABLET	ORAL	Y
dabigatran etexilate mesylate	PRADAXA	CAPSULE	ORAL	Y
dalteparin sodium,porcine	FRAGMIN	SYRINGE	SUB-Q	Y
edoxaban tosylate	SAVAYSA	TABLET	ORAL	Y
enoxaparin sodium	ENOXAPARIN SODIUM	SYRINGE	SUB-Q	Y
enoxaparin sodium	LOVENOX	SYRINGE	SUB-Q	Y
enoxaparin sodium	ENOXAPARIN SODIUM	VIAL	SUB-Q	Y
enoxaparin sodium	LOVENOX	VIAL	SUB-Q	Y
rivaroxaban	XARELTO	TAB DS PK	ORAL	Y
rivaroxaban	XARELTO	TABLET	ORAL	Y
warfarin sodium	COUMADIN	TABLET	ORAL	Y
warfarin sodium	JANTOVEN	TABLET	ORAL	Y
warfarin sodium	WARFARIN SODIUM	TABLET	ORAL	Y
betrixaban maleate	BEVYXXA	CAPSULE	ORAL	N
dalteparin sodium,porcine	FRAGMIN	VIAL	SUB-Q	N
enoxaparin sodium	LOVENOX	AMPUL	SUB-Q	N
fondaparinux sodium	ARIXTRA	SYRINGE	SUB-Q	N
fondaparinux sodium	FONDAPARINUX SODIUM	SYRINGE	SUB-Q	N

Appendix 2: Abstracts of Comparative Clinical Trials

Aspirin or Rivaroxaban for VTE Prophylaxis after Hip or Knee Arthroplasty.

Anderson DR, Dunbar M, Murnaghan J, Kahn SR, Gross P, Forsythe M, Pelet S, Fisher W, Belzile E, Dolan S, Crowther M, Bohm E, MacDonald SJ, Gofton W, Kim P, Zukor D, Pleasance S, Andreou P, Doucette S, Theriault C, Abianui A, Carrier M, Kovacs MJ, Rodger MA, Coyle D, Wells PS, Vendittoli PA

BACKGROUND:

Clinical trials and meta-analyses have suggested that aspirin may be effective for the prevention of venous thromboembolism (proximal deep-vein thrombosis or pulmonary embolism) after total hip or total knee arthroplasty, but comparisons with direct oral anticoagulants are lacking for prophylaxis beyond hospital discharge.

METHODS:

We performed a multicenter, double-blind, randomized, controlled trial involving patients who were undergoing total hip or knee arthroplasty. All the patients received once-daily oral rivaroxaban (10 mg) until postoperative day 5 and then were randomly assigned to continue rivaroxaban or switch to aspirin (81 mg daily) for an additional 9 days after total knee arthroplasty or for 30 days after total hip arthroplasty. Patients were followed for 90 days for symptomatic venous thromboembolism (the primary effectiveness outcome) and bleeding complications, including major or clinically relevant nonmajor bleeding (the primary safety outcome).

RESULTS:

A total of 3424 patients (1804 undergoing total hip arthroplasty and 1620 undergoing total knee arthroplasty) were enrolled in the trial. Venous thromboembolism occurred in 11 of 1707 patients (0.64%) in the aspirin group and in 12 of 1717 patients (0.70%) in the rivaroxaban group (difference, 0.06 percentage points; 95% confidence interval [CI], -0.55 to 0.66; P<0.001 for noninferiority and P=0.84 for superiority). Major bleeding complications occurred in 8 patients (0.47%) in the aspirin group and in 5 (0.29%) in the rivaroxaban group (difference, 0.18 percentage points; 95% CI, -0.65 to 0.29; P=0.42). Clinically important bleeding occurred in 22 patients (1.29%) in the aspirin group and in 17 (0.99%) in the rivaroxaban group (difference, 0.30 percentage points; 95% CI, -1.07 to 0.47; P=0.43).

CONCLUSIONS:

Among patients who received 5 days of rivaroxaban prophylaxis after total hip or total knee arthroplasty, extended prophylaxis with aspirin was not significantly different from rivaroxaban in the prevention of symptomatic venous thromboembolism. (Funded by the Canadian Institutes of Health Research; ClinicalTrials.gov number, NCT01720108 .).

Uninterrupted Dabigatran versus Warfarin for Ablation in Atrial Fibrillation.

Calkins H, Willems S, Gerstenfeld EP, Verma A, Schilling R, Hohnloser SH, Okumura K, Serota H, Nordaby M, Guiver K, Biss B, Brouwer MA, Grimaldi M; RE-CIRCUIT Investigators.

BACKGROUND:

Catheter ablation of atrial fibrillation is typically performed with uninterrupted anticoagulation with warfarin or interrupted non-vitamin K antagonist oral anticoagulant therapy. Uninterrupted anticoagulation with a non-vitamin K antagonist oral anticoagulant, such as dabigatran, may be safer; however, controlled data are lacking. We investigated the safety of uninterrupted dabigatran versus warfarin in patients undergoing ablation of atrial fibrillation.

METHODS:

In this randomized, open-label, multicenter, controlled trial with blinded adjudicated end-point assessments, we randomly assigned patients scheduled for catheter ablation of paroxysmal or persistent atrial fibrillation to receive either dabigatran (150 mg twice daily) or warfarin (target international normalized

ratio, 2.0 to 3.0). Ablation was performed after 4 to 8 weeks of uninterrupted anticoagulation, which was continued during and for 8 weeks after ablation. The primary end point was the incidence of major bleeding events during and up to 8 weeks after ablation; secondary end points included thromboembolic and other bleeding events.

RESULTS:

The trial enrolled 704 patients across 104 sites; 635 patients underwent ablation. Baseline characteristics were balanced between treatment groups. The incidence of major bleeding events during and up to 8 weeks after ablation was lower with dabigatran than with warfarin (5 patients [1.6%] vs. 22 patients [6.9%]; absolute risk difference, -5.3 percentage points; 95% confidence interval, -8.4 to -2.2; P<0.001). Dabigatran was associated with fewer periprocedural pericardial tamponades and groin hematomas than warfarin. The two treatment groups had a similar incidence of minor bleeding events. One thromboembolic event occurred in the warfarin group.

CONCLUSIONS:

In patients undergoing ablation for atrial fibrillation, anticoagulation with uninterrupted dabigatran was associated with fewer bleeding complications than uninterrupted warfarin. (Funded by Boehringer Ingelheim; RE-CIRCUIT ClinicalTrials.gov number, NCT02348723 .).

Dabigatran for Prevention of Stroke after Embolic Stroke of Undetermined Source.

Diener HC, Sacco RL, Easton JD, Granger CB, Bernstein RA, Uchiyama S, Kreuzer J, Cronin L, Cotton D, Grauer C, Brueckmann M, Chernyatina M, Donnan G, Ferro JM, Grond M, Kallmünzer B, Krupinski J, Lee BC, Lemmens R, Masjuan J, Odinak M, Saver JL, Schellinger PD, Toni D, Toyoda K; RE-SPECT ESUS Steering Committee and Investigators.

BACKGROUND:

Cryptogenic strokes constitute 20 to 30% of ischemic strokes, and most cryptogenic strokes are considered to be embolic and of undetermined source. An earlier randomized trial showed that rivaroxaban is no more effective than aspirin in preventing recurrent stroke after a presumed embolic stroke from an undetermined source. Whether dabigatran would be effective in preventing recurrent strokes after this type of stroke was unclear.

METHODS:

We conducted a multicenter, randomized, double-blind trial of dabigatran at a dose of 150 mg or 110 mg twice daily as compared with aspirin at a dose of 100 mg once daily in patients who had had an embolic stroke of undetermined source. The primary outcome was recurrent stroke. The primary safety outcome was major bleeding.

RESULTS:

A total of 5390 patients were enrolled at 564 sites and were randomly assigned to receive dabigatran (2695 patients) or aspirin (2695 patients). During a median follow-up of 19 months, recurrent strokes occurred in 177 patients (6.6%) in the dabigatran group (4.1% per year) and in 207 patients (7.7%) in the aspirin group (4.8% per year) (hazard ratio, 0.85; 95% confidence interval [CI], 0.69 to 1.03; P = 0.10). Ischemic strokes occurred in 172 patients (4.0% per year) and 203 patients (4.7% per year), respectively (hazard ratio, 0.84; 95% CI, 0.68 to 1.03). Major bleeding occurred in 77 patients (1.7% per year) in the dabigatran group and in 64 patients (1.4% per year) in the aspirin group (hazard ratio, 1.19; 95% CI, 0.85 to 1.66). Clinically relevant nonmajor bleeding occurred in 70 patients (1.6% per year) and 41 patients (0.9% per year), respectively.

CONCLUSIONS:

In patients with a recent history of embolic stroke of undetermined source, dabigatran was not superior to aspirin in preventing recurrent stroke. The incidence of major bleeding was not greater in the dabigatran group than in the aspirin group, but there were more clinically relevant nonmajor bleeding events in the dabigatran group. (Funded by Boehringer Ingelheim; RE-SPECT ESUS ClinicalTrials.gov number, NCT02239120.).

Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease.

Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, Diaz R, Alings M, Lonn EM, Anand SS, Widimsky P, Hori M, Avezum A, Piegas LS, Branch KRH, Probstfield J, Bhatt DL, Zhu J, Liang Y, Maggioni AP, Lopez-Jaramillo P, O'Donnell M, Kakkar AK, Fox KAA, Parkhomenko AN, Ertl G, Störk S, Keltai M, Ryden L, Pogosova N, Dans AL, Lanas F, Commerford PJ, Torp-Pedersen C, Guzik TJ, Verhamme PB, Vinereanu D, Kim JH, Tonkin AM, Lewis BS, Felix C, Yusoff K, Steg PG, Metsarinne KP, Cook Bruns N, Misselwitz F, Chen E, Leong D, Yusuf S; COMPASS Investigators.

BACKGROUND:

We evaluated whether rivaroxaban alone or in combination with aspirin would be more effective than aspirin alone for secondary cardiovascular prevention.

METHODS:

In this double-blind trial, we randomly assigned 27,395 participants with stable atherosclerotic vascular disease to receive rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg once daily), rivaroxaban (5 mg twice daily), or aspirin (100 mg once daily). The primary outcome was a composite of cardiovascular death, stroke, or myocardial infarction. The study was stopped for superiority of the rivaroxaban-plus-aspirin group after a mean follow-up of 23 months.

RESULTS:

The primary outcome occurred in fewer patients in the rivaroxaban-plus-aspirin group than in the aspirin-alone group (379 patients [4.1%] vs. 496 patients [5.4%]; hazard ratio, 0.76; 95% confidence interval [CI], 0.66 to 0.86; P<0.001; z=-4.126), but major bleeding events occurred in more patients in the rivaroxaban-plus-aspirin group (288 patients [3.1%] vs. 170 patients [1.9%]; hazard ratio, 1.70; 95% CI, 1.40 to 2.05; P<0.001). There was no significant difference in intracranial or fatal bleeding between these two groups. There were 313 deaths (3.4%) in the rivaroxaban-plus-aspirin group as compared with 378 (4.1%) in the aspirin-alone group (hazard ratio, 0.82; 95% CI, 0.71 to 0.96; P=0.01; threshold P value for significance, 0.0025). The primary outcome did not occur in significantly fewer patients in the rivaroxaban-alone group than in the aspirin-alone group, but major bleeding events occurred in more patients in the rivaroxaban-alone group.

CONCLUSIONS:

Among patients with stable atherosclerotic vascular disease, those assigned to rivaroxaban (2.5 mg twice daily) plus aspirin had better cardiovascular outcomes and more major bleeding events than those assigned to aspirin alone. Rivaroxaban (5 mg twice daily) alone did not result in better cardiovascular outcomes than aspirin alone and resulted in more major bleeding events. (Funded by Bayer; COMPASS ClinicalTrials.gov number, NCT01776424 .).

Edoxaban versus enoxaparin-warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): a randomised, open-label, phase 3b trial.

Goette A, Merino JL, Ezekowitz MD, Zamoryakhin D, Melino M, Jin J, Mercuri MF, Grosso MA, Fernandez V, Al-Saady N, Pelekh N, Merkely B, Zenin S, Kushnir M, Spinar J, Batushkin V, de Groot JR, Lip GY; ENSURE-AF investigators.

BACKGROUND:

Edoxaban, an oral factor Xa inhibitor, is non-inferior for prevention of stroke and systemic embolism in patients with atrial fibrillation and is associated with less bleeding than well controlled warfarin therapy. Few safety data about edoxaban in patients undergoing electrical cardioversion are available.

METHODS:

We did a multicentre, prospective, randomised, open-label, blinded-endpoint evaluation trial in 19 countries with 239 sites comparing edoxaban 60 mg per day with enoxaparin-warfarin in patients undergoing electrical cardioversion of non-valvular atrial fibrillation. The dose of edoxaban was reduced to 30 mg per day if one or more factors (creatinine clearance 15-50 mL/min, low bodyweight [≤60 kg], or concomitant use of P-glycoprotein inhibitors) were present. Block randomisation (block size four)-stratified by cardioversion approach (transoesophageal echocardiography [TEE] or not), anticoagulant experience, selected edoxaban dose, and region-was done through a voice-web system. The primary efficacy endpoint was a composite of stroke, systemic embolic event, myocardial infarction, and cardiovascular mortality, analysed by intention to treat. The primary safety endpoint was major and clinically relevant non-major

(CRNM) bleeding in patients who received at least one dose of study drug. Follow-up was 28 days on study drug after cardioversion plus 30 days to assess safety. This trial is registered with ClinicalTrials.gov, number NCT02072434.

FINDINGS:

Between March 25, 2014, and Oct 28, 2015, 2199 patients were enrolled and randomly assigned to receive edoxaban (n=1095) or enoxaparin-warfarin (n=1104). The mean age was 64 years (SD 10·54) and mean CHA_2DS_2-VASc score was 2·6 (SD 1·4). Mean time in therapeutic range on warfarin was 70·8% (SD 27·4). The primary efficacy endpoint occurred in five (<1%) patients in the edoxaban group versus 11 (1%) in the enoxaparin-warfarin group (odds ratio [OR] 0·46, 95% CI 0·12-1·43). The primary safety endpoint occurred in 16 (1%) of 1067 patients given edoxaban versus 11 (1%) of 1082 patients given enoxaparin-warfarin (OR 1·48, 95% CI 0·64-3·55). The results were independent of the TEE-guided strategy and anticoagulation status.

INTERPRETATION:

ENSURE-AF is the largest prospective randomised clinical trial of anticoagulation for cardioversion of patients with non-valvular atrial fibrillation. Rates of major and CRNM bleeding and thromboembolism were low in the two treatment groups.

Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source.

Hart RG, Sharma M, Mundl H, Kasner SE, Bangdiwala SI, Berkowitz SD, Swaminathan B, Lavados P, Wang Y, Wang Y, Davalos A, Shamalov N, Mikulik R, Cunha L, Lindgren A, Arauz A, Lang W, Czlonkowska A, Eckstein J, Gagliardi RJ, Amarenco P, Ameriso SF, Tatlisumak T, Veltkamp R, Hankey GJ, Toni D, Bereczki D, Uchiyama S, Ntaios G, Yoon BW, Brouns R, Endres M, Muir KW, Bornstein N, Ozturk S, O'Donnell MJ, De Vries Basson MM, Pare G, Pater C, Kirsch B, Sheridan P, Peters G, Weitz JI, Peacock WF, Shoamanesh A, Benavente OR, Joyner C, Themeles E, Connolly SJ; NAVIGATE ESUS Investigators.

BACKGROUND:

Embolic strokes of undetermined source represent 20% of ischemic strokes and are associated with a high rate of recurrence. Anticoagulant treatment with rivaroxaban, an oral factor Xa inhibitor, may result in a lower risk of recurrent stroke than aspirin.

METHODS:

We compared the efficacy and safety of rivaroxaban (at a daily dose of 15 mg) with aspirin (at a daily dose of 100 mg) for the prevention of recurrent stroke in patients with recent ischemic stroke that was presumed to be from cerebral embolism but without arterial stenosis, lacune, or an identified cardioembolic source. The primary efficacy outcome was the first recurrence of ischemic or hemorrhagic stroke or systemic embolism in a time-to-event analysis; the primary safety outcome was the rate of major bleeding.

RESULTS:

A total of 7213 participants were enrolled at 459 sites; 3609 patients were randomly assigned to receive rivaroxaban and 3604 to receive aspirin. Patients had been followed for a median of 11 months when the trial was terminated early because of a lack of benefit with regard to stroke risk and because of bleeding associated with rivaroxaban. The primary efficacy outcome occurred in 172 patients in the rivaroxaban group (annualized rate, 5.1%) and in 160 in the aspirin group (annualized rate, 4.8%) (hazard ratio, 1.07; 95% confidence interval [CI], 0.87 to 1.33; P=0.52). Recurrent ischemic stroke occurred in 158 patients in the rivaroxaban group (annualized rate, 4.7%) and in 156 in the aspirin group (annualized rate, 4.7%). Major bleeding occurred in 62 patients in the rivaroxaban group (annualized rate, 1.8%) and in 23 in the aspirin group (annualized rate, 0.7%) (hazard ratio, 2.72; 95% CI, 1.68 to 4.39; P<0.001).

CONCLUSIONS:

Rivaroxaban was not superior to aspirin with regard to the prevention of recurrent stroke after an initial embolic stroke of undetermined source and was associated with a higher risk of bleeding. (Funded by Bayer and Janssen Research and Development; NAVIGATE ESUS ClinicalTrials.gov number, NCT02313909 .).

Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation.

Lopes RD, Heizer G, Aronson R, Vora AN, Massaro T, Mehran R, Goodman SG, Windecker S, Darius H, Li J, Averkov O, Bahit MC, Berwanger O, Budaj A, Hijazi Z, Parkhomenko A, Sinnaeve P, Storey RF, Thiele H, Vinereanu D, Granger CB, Alexander JH; AUGUSTUS Investigators.

BACKGROUND:

Appropriate antithrombotic regimens for patients with atrial fibrillation who have an acute coronary syndrome or have undergone percutaneous coronary intervention (PCI) are unclear.

METHODS:

In an international trial with a two-by-two factorial design, we randomly assigned patients with atrial fibrillation who had an acute coronary syndrome or had undergone PCI and were planning to take a $P2Y_{12}$ inhibitor to receive apixaban or a vitamin K antagonist and to receive aspirin or matching placebo for 6 months. The primary outcome was major or clinically relevant nonmajor bleeding. Secondary outcomes included death or hospitalization and a composite of ischemic events.

RESULTS:

Enrollment included 4614 patients from 33 countries. There were no significant interactions between the two randomization factors on the primary or secondary outcomes. Major or clinically relevant nonmajor bleeding was noted in 10.5% of the patients receiving apixaban, as compared with 14.7% of those receiving a vitamin K antagonist (hazard ratio, 0.69; 95% confidence interval [CI], 0.58 to 0.81; P<0.001 for both noninferiority and superiority), and in 16.1% of the patients receiving aspirin, as compared with 9.0% of those receiving placebo (hazard ratio, 1.89; 95% CI, 1.59 to 2.24; P<0.001). Patients in the apixaban group had a lower incidence of death or hospitalization than those in the vitamin K antagonist group (23.5% vs. 27.4%; hazard ratio, 0.83; 95% CI, 0.74 to 0.93; P = 0.002) and a similar incidence of ischemic events. Patients in the aspirin group had an incidence of death or hospitalization and of ischemic events that was similar to that in the placebo group.

CONCLUSIONS:

In patients with atrial fibrillation and a recent acute coronary syndrome or PCI treated with a $P2Y_{12}$ inhibitor, an antithrombotic regimen that included apixaban, without aspirin, resulted in less bleeding and fewer hospitalizations without significant differences in the incidence of ischemic events than regimens that included a vitamin K antagonist, aspirin, or both. (Funded by Bristol-Myers Squibb and Pfizer; AUGUSTUS ClinicalTrials.gov number, NCT02415400.).

Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism.

Weitz JI, Lensing AWA, Prins MH, Bauersachs R, Beyer-Westendorf J, Bounameaux H, Brighton TA, Cohen AT, Davidson BL, Decousus H, Freitas MCS, Holberg G, Kakkar AK, Haskell L, van Bellen B, Pap AF, Berkowitz SD, Verhamme P, Wells PS, Prandoni P; EINSTEIN CHOICE Investigators.

BACKGROUND:

Although many patients with venous thromboembolism require extended treatment, it is uncertain whether it is better to use full- or lower-intensity anticoagulation therapy or aspirin.

METHODS:

In this randomized, double-blind, phase 3 study, we assigned 3396 patients with venous thromboembolism to receive either once-daily rivaroxaban (at doses of 20 mg or 10 mg) or 100 mg of aspirin. All the study patients had completed 6 to 12 months of anticoagulation therapy and were in equipoise regarding the need for continued anticoagulation. Study drugs were administered for up to 12 months. The primary efficacy outcome was symptomatic recurrent fatal or nonfatal venous thromboembolism, and the principal safety outcome was major bleeding.

RESULTS:
A total of 3365 patients were included in the intention-to-treat analyses (median treatment duration, 351 days). The primary efficacy outcome occurred in 17 of 1107 patients (1.5%) receiving 20 mg of rivaroxaban and in 13 of 1127 patients (1.2%) receiving 10 mg of rivaroxaban, as compared with 50 of 1131 patients (4.4%) receiving aspirin (hazard ratio for 20 mg of rivaroxaban vs. aspirin, 0.34; 95% confidence interval [CI], 0.20 to 0.59; hazard ratio for 10 mg of rivaroxaban vs. aspirin, 0.26; 95% CI, 0.14 to 0.47; P<0.001 for both comparisons). Rates of major bleeding were 0.5% in the group receiving 20 mg of rivaroxaban, 0.4% in the group receiving 10 mg of rivaroxaban, and 0.3% in the aspirin group; the rates of clinically relevant nonmajor bleeding were 2.7%, 2.0%, and 1.8%, respectively. The incidence of adverse events was similar in all three groups.
CONCLUSIONS:
Among patients with venous thromboembolism in equipoise for continued anticoagulation, the risk of a recurrent event was significantly lower with rivaroxaban at either a treatment dose (20 mg) or a prophylactic dose (10 mg) than with aspirin, without a significant increase in bleeding rates. (Funded by Bayer Pharmaceuticals; EINSTEIN CHOICE ClinicalTrials.gov number, NCT02064439 .)

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R)** 1946 to September Week 1 2019

Search Strategy:

#	Searches	Results
1	apixaban.mp.	2433
2	dabigatran.mp. or Dabigatran/	4075
3	dalteparin.mp. or Dalteparin/	1214
4	edoxaban.mp.	990
5	enoxaparin.mp. or Enoxaparin/	4572
6	rivaroxaban.mp. or Rivaroxaban/	3960
7	warfarin.mp. or Warfarin/	26192
8	betrixaban.mp.	119
9	fondaparinux.mp. or Fondaparinux/	1692
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	35726
11	limit 10 to (english language and humans and yr="2017 -Current")	3766
12	limit 11 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	236

Appendix 4: Key Inclusion Criteria

Population	Patients requiring anticoagulation
Intervention	Anticoagulant therapy
Comparator	Active control or placebo
Outcomes	Mortality, stroke, recurrent VTE, DVT, PE, bleeding
Timing	Treatment or prophylaxis
Setting	Inpatient or outpatient

ProDUR Report for July through September 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	2	1	0	1	0.01%	50.0%
DC (Drug/Inferred Disease Interaction)	Quetiapine billed and condition on file for Congenital Long QT Sundrome	Set alert/Pay claim	1,340	279	0	1,061	1.30%	20.8%
DD (Drug/Drug Interaction)	Linezolid being billed and patient is on an SNRI	Set alert/Pay claim	108	23	0	85	0.08%	21.3%
ER (Early Refill)	Previously filled 30 day supply and trying to refill after 20 days (80% = 24 days)	Set alert/Deny claim	66,284	11,287	58	54,932	68.37%	17.0%
ID (Ingredient Duplication)	Oxycodone IR 15mg billed and patient had Oxycodone 40mg ER filled in past month	Set alert/Pay claim	20,565	4,963	6	15,576	21.13%	24.1%
LD (Low Dose)	Divalproex 500mg ER billed for 250mg daily (#15 tabs for 30 day supply)	Set alert/Pay claim	657	111	0	544	0.63%	16.9%
MC (Drug/Disease Interaction)	Bupropion being billed and patient has a seizure disorder	Set alert/Pay claim	837	193	0	644	0.83%	23.1%
MX (Maximum Duration of Therapy)		Set alert/Pay claim	451	121	1	329	0.40%	26.8%
PG (Pregnancy/Drug Interaction)	Accutane billed and client has recent diagnosis history of pregnancy	Set alert/Deny claim	25	16	0	9	0.02%	64.0%
TD (Therapeutic Duplication)	Diazepam being billed and patient recently filled an Alprazolam claim.	Set alert/Pay claim	6,702	1,770	0	4,924	6.83%	26.4%
		Totals	**96,971**	**18,764**	**65**	**78,105**	**99.60%**	**19.4%**

ProDUR Report for July through September 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)	1,260	189	1,071	10,772	11.7%	15.0%
ER	Lorazepam	351	87	264	11,741	3.0%	24.8%
ER	Alprazolam	235	40	195	8,092	2.9%	17.0%
ER	Diazepam	136	37	99	4,542	3.0%	27.2%
ER	Buspirone (Buspar)	2,219	329	1,890	24,121	9.2%	14.8%
ER	Lamictal (Lamotrigine)	3,941	725	3,216	33,502	11.8%	18.4%
ER	Seroquel (Quetiapine)	3,288	679	2,609	23,829	13.8%	20.7%
ER	Risperdal (Risperidone)	1,663	287	1,376	12,335	13.5%	17.3%
ER	Abilify (Aripiprazole)	2,407	364	2,043	19,677	12.2%	15.1%
ER	Wellbutrin (Bupropion)	4,161	666	3,495	47,888	8.7%	16.0%
ER	Hydrocodone/APAP	26	5	21	2,248	1.2%	19.2%
ER	Oxycodone	46	18	28	1,611	2.9%	**39.1%**
ER	Oxycodone/APAP	14	3	11	663	2.1%	21.4%
ER	Tramadol	16	5	11	608	2.6%	31.3%
ER	Buprenorphine/Naloxone	95	36	59	2,073	4.6%	**37.9%**
ER	Zoloft (Sertraline)	4,944	833	4,111	51,600	9.6%	16.8%
ER	Prozac (Fluoxetine)	3,787	555	3,232	39,975	9.5%	14.7%
ER	Lexapro (Escitalopram)	2,801	407	2,394	31,219	9.0%	14.5%
ER	Celexa (Citalopram)	2,038	271	1,767	23,843	8.5%	13.3%
ER	Trazodone	4,600	655	3,943	44,585	10.3%	14.2%

ProDUR Report for July through September 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	July	2,924	167	277	817	3	1,577	0	83
ER	August	3,220	138	311	935	2	1,710	0	124
ER	September	827	28	91	223	3	439	0	43
	Total =	**6,971**	**333**	**679**	**1,975**	**8**	**3,726**	**0**	**250**
	Percentage of total overrides =		**4.8%**	**9.7%**	**28.3%**	**0.1%**	**53.5%**	**0.0%**	**3.6%**

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	60
		Total Faxes Successfully Sent	35	48	30	20
		Prescriptions Changed to Recommended Dose Within 3 Months of Fax Sent	29	29	10	3
		Prescriptions Changed to Alternative Dose Within 3 Months of Fax Sent	6	26	9	
		Prescriptions Unchanged after 3 Months of Fax Sent	50	42	26	
		Safety Monitoring Profiles Identified	3	2	7	
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Faxes Sent	$61,216	$51,126	$16,177	$2,931

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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
Expert Consultation Referral	Antipsychotic Use in Children	Total patients identified				412
		Profiles sent for expert review				47

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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	44
		Total prescribers identified			22	44
		Prescribers successfully notified			22	43
		Patients with claims for the same antipsychotic within the next 90 days			6	13
		Patients with claims for a different antipsychotic within the next 90 days				2

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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	35
	Children under age 18 on 3 or more psychotropics	RetroDUR_Profiles Reviewed	9	5	16	3
	Children under age 18 on any psychotropic	RetroDUR_Profiles Reviewed	85	110	120	42
	Children under age 6 on any psychotropic	RetroDUR_Profiles Reviewed	5	7	14	5
	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	25
		RetroDUR_Letters Sent To Providers	5	2	3	1
		Provider Responses	2	0	0	0
		Provider Agreed / Found Info Useful	2	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	11
		RetroDUR_Letters Sent To Providers	5	6	21	3
		Provider Responses	0	0	2	2
		Provider Agreed / Found Info Useful	0	0	2	2

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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
Safety Net	ICS/LABA	Disqualified	24	20	29	11
		Disqualified - No Provider Info	1			
		Disqualified - Erroneous denial	23	20	29	11
		Faxes Sent	7	9	8	2
		Fax Sent - SABA	3	3	3	
		Fax Sent - Combination Inhaler	3	5	3	
		Fax Sent - Controller	1		1	
		No Subsequent Pulmonary Claims		1	1	2

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July 2019 Volume 9, Issue 5

Oregon Health Authority Mental Health Clinical Advisory Group (MHCAG) Recommendations for the Treatment of Schizophrenia

Kathy Sentena, Pharm. D., Drug Use and Research Management Program, Oregon State University College of Pharmacy

There is an expansive need for quality behavioral and mental health services across Oregon. In response, the 2017 Oregon Legislature passed House Bill 2300 which directs the Oregon Health Authority (OHA) to convene a Mental Health Clinical Advisory Group (MHCAG) to develop evidence-based treatment algorithms.[1] Their recommendations are designed to improve access to care for medication assistance recipients with behavioral health disorders and to standardize treatment recommendations. In March of 2019, the MHCAG released their first set of recommendations focusing on the treatment of schizophrenia.[1] This newsletter will summarize their recommendations, describe opportunities with the Oregon Psychiatric Access Line (OPAL) and provide cost-comparison data.

MHCAG Schizophrenia Treatment Recommendations

The MHCAG was asked to develop criteria for managing schizophrenia, specifically focusing on the following:

- Efficacy of the drug
- Cost of the drug
- Potential drug side effects
- Patient's history of the drug

The group advocates for a collaborative approach between providers and patients to choose evidence-based medication therapies that provide efficacy and value.[1] Previous reviews of the literature have found a lack of high-quality evidence in differences between the comparative efficacy or harms, or benefits of oral versus injectable dosage forms, of antipsychotics in the management of schizophrenia.[2] Therefore, MHCAG recommendations were based on evidence and incorporation of expert opinion.

The MHCAG recommendations for schizophrenia are separated into: 1. acute psychosis and 2. stabilization and management.[1] Medications are an integral component of both scenarios. Factors that assist in choosing the most appropriate treatment are based on patient response and adherence to their current medication regimen.[1] The MHCAG treatment algorithms are divided into: starting second generation antipsychotics, use of first generation antipsychotics and alternative medication treatments in schizophrenia.

Antipsychotic recommendations are based on therapies that provide the greatest value and cost-effectiveness.[1] First-line treatment recommendations for generic second-generation antipsychotics include aripiprazole, risperidone, or paliperidone.[1] These agents are available as both oral formulation and long-acting injectable (LAI). Due to its improved safety profile, aripiprazole is recommended for patients who want to minimize the following:

- Weight gain and diabetes
- Pseudoparkinsonism and tardive dyskinesia
- High cholesterol
- Prolactin elevation

Risperidone or paliperidone are recommended for patients who want to minimize the risk of:

- Akathisia
- Treatment emergent activation or agitation

Patients who have an inadequate response after 2 to 6 weeks of therapy should switch to one of the other first-line treatments.[1] If an adequate response is obtained after 2 to 4 weeks then a LAI can be considered, especially in those patients who have the potential for nonadherence or a history of serious antipsychotic episodes that resulted in admission (**Table 1**). Additionally, LAIs are associated with a higher cost, which could be a potential barrier for some patients (**Figure 1**). Long-acting injectables should only be started if the patient has used the oral form and received a benefit with no or tolerable side effects.[1] The dose of LAI should be approximated based on the oral medication dose. Depending on the LAI, the oral form may be discontinued immediately or continued for 2 to 4 weeks.[1]

Table 1. Long-acting Second Generation Antipsychotic Injectables[1,3]

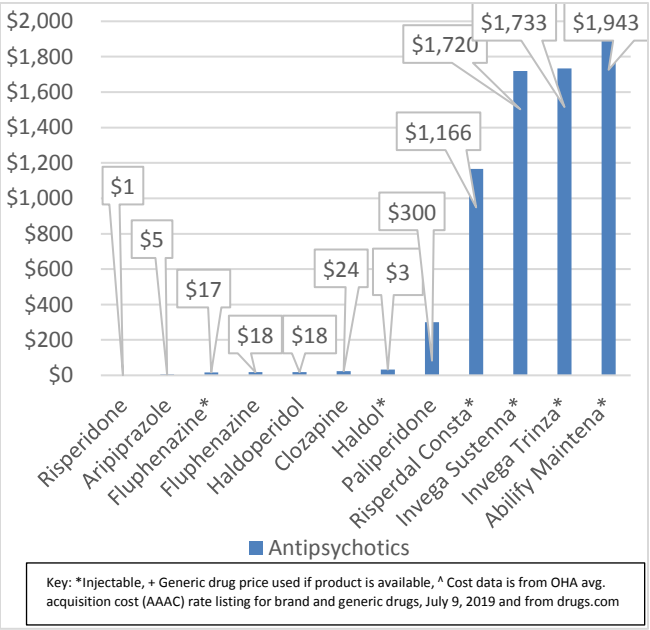
Generic Name*	Brand Name	Maintenance Dosing Interval	Oral supplementation during LAI initiation
Aripiprazole	Abilify Maintena®	Monthly	14 days of concurrent oral antipsychotic
Aripiprazole lauroxil	Aristada®	Monthly, every 6 weeks or every 8 weeks	A single 30 mg oral aripiprazole dose‡ or 21 days of oral aripiprazole
Risperidone	Risperdal Consta®	Every 2 weeks	3 weeks of concurrent oral antipsychotic
Paliperidone	Invega Sustenna®	Monthly	None

Paliperidone pamitate	Invega Trinza®	Once every 3 months	None
Risperidone	Perseris®)	Monthly	None

Abbreviation: LAI – long-acting injectables
* All treatments are preferred therapies on the OHA preferred drug list
ǂ In conjunction with Aristada Initio injection

Patients with predominately positive symptoms and need to minimize cardiometabolic risk, may be considered for a first generation antipsychotic. Fluphenazine or haldoperiodol are recommended first-line by the algorithm.[1] Two to four weeks of therapy are required to determine if an adequate response is obtained. If appropriate, a 2-week LAI (fluphenazine) or 4-week LAI (haldoperidol or Haldol Decanoate®) may be an option.[1]
If the patient fails two first-line therapies, of either first or second generation antipsychotic, then clozapine is recommended.[1] Clozapine is a viable alternative even though it is often underutilized due to monitoring requirements and risk of adverse reactions (e.g., central nervous system [CNS] and agranulocytosis). A six month trial is required to determine an adequate response to clozapine. Clozapine should not be used in patients with a history of clozapine-induced agranulocytosis, severe CNS depression or delirium, coma, history of clozapine-induced myocarditis or cardiomyopathy, pretreatment absolute neutrophil count (ANC) less than 1500 cells/cubic mm^3, uncontrolled seizure disorder or inability to adhere to lab monitoring.[1] Clozapine is also associated with multiple drug interactions mediated through cytochrome P450 enzymes and a full review of the patient's medication profile should be completed before drug initiation. Comparative costs of select antipsychotics are presented in **Figure 1**.

Figure 1. Thirty-Day Cost of Common Antipsychotics+^



Key: *Injectable, + Generic drug price used if product is available, ^ Cost data is from OHA avg. acquisition cost (AAAC) rate listing for brand and generic drugs, July 9, 2019 and from drugs.com

Antipsychotic use may cause serious and/or bothersome adverse reactions, which may be minimized by using the lowest effective dose. Regular laboratory monitoring (e.g., hemoglobin A1c [HbA1c], complete blood count [CBC], lipids, thyroid screen) will aid in detection and management of potential adverse reactions.[1] Patients should be monitored for indicators of parkinsonism, acute dystonia, akathisia and tardive dyskinesia.[1] Validated assessment tools and detailed options for the management of adverse reactions associated with antipsychotics are available in the full MHCAG report.[1]

Dosing Management

The MHCAG recommends that a 6 to 8 week titration up to the maximum tolerated antipsychotic dose is considered an adequate trial for acute treatment.[1] The FDA maximum daily dose should not be exceeded. Patients who have been stable on a medication regimen for 6 to 12 months can be considered for dosage reduction and possibly discontinuation of their antipsychotic. A maintenance dose of an antipsychotic is often lower than the acute treatment dose. The general recommendation for dose lowering is to gradually decrease the dose over 3 months until medication is discontinued or symptoms of psychosis return.[1] Clozapine can be associated with rebound psychosis, and therefore, should be tapered slowly. Tapering LAI can be difficult because clinical changes often lag 1 to 3 months after a dose has been changed. Oral supplementation may be needed for symptom reoccurrence.[1]

The Oregon Psychiatric Access Line (OPAL)

Optimal management of patients with behavioral mental health conditions often requires utilization of a variety of health care resources. In additional to standardized care through treatment algorithms, access to psychiatric consultation is a vital resource to improve care. The Oregon Psychiatric Access Line offers medication consultation for providers provided by Oregon Health and Science University (OHSU).[1] The purpose of OPAL is to allow high quality behavioral advice for Oregon youth and adults via timely psychiatric consultation, medical practitioner education and connections with mental health professionals throughout the state.[2] Providers must register with OPAL, which allows access to the following services:

- Free, same-day adult and child psychiatrist phone consultation
- Medical practitioner education
- Connection to mental health professionals around the state of Oregon

OPAL Consultation Line
Phone: 503-346-1000 (providers only)
Web: www.ohsu.edu/school-of-medicine/child-and-adolescent-psychiatry/oregon-psychiatric-access-line

Conclusion

There are many opportunities for improvements in the care and treatment of behavioral health conditions in the state of Oregon. The recommendations provided by MHCAG, along with the collaborative expertise provided by OPAL, is a viable pathway to improve the access and quality of care provided to patients with schizophrenia. Treatment algorithms and detailed guidance on the recommendations summarized in this newsletter are available at: https://apps.state.or.us/Forms/Served/le7548.pdf .[1]

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Stimulant Use in Excessive Somnolence Disorders

Victor Rojo, Pharm.D. Candidate, 2020

Excessive daytime sleepiness (EDS), that interferes with an individual's daily activities has a direct impact on the quality of life of patients, as it can affect social aspects, occupation, education, and functional status (i.e. increased risk of traffic accidents while driving).[1] Approximately 20% of the general population is afflicted with EDS, although consistency in defining, measuring, and evaluating daytime sleepiness has not been clearly defined.[2] Funded conditions associated with EDS include sleep apnea, narcolepsy and cataplexy. General hypersomnia is unfunded by the Oregon Health Authority (OHA) as primary first line therapies for hypersomnia often rely on treatment of the underlying comorbid condition, lifestyle changes, and non-pharmacological interventions. The purpose of this newsletter is to explore and compare pharmacologic treatment options for EDS associated with narcolepsy or obstructive sleep apnea (OSA) unresponsive to sleep hygiene or nonpharmacological therapies.

EDS is evaluated by a variety of metrics including the maintenance of wakefulness test (MWT), which examines a patient's capacity to combat sleepiness in a calming and neutral laboratory setting, and Epworth Sleepiness Scale (ESS), which is a patient-rated subjective score of theoretical scenarios measuring the likelihood the patient would fall asleep.[3,4] There is no evidence to suggest changes in MWT correlate with improvement in patient outcomes. Changes in ESS are considered clinically meaningful with a reduction of at least 25%.[5,6] Both of these metrics are commonly used as endpoints in clinical trials, though it is uncertain if either endpoint correlates with realistic improvements in quality of life. The goal of therapy is to increase alertness during "normal" waking hours to allow a better coordination for work, school, driving, and other social and behavioral activities.

Pharmacologic Treatments for Excessive Daytime Sleepiness

Commonly used drugs for EDS include dopamine reuptake inhibitors (modafinil, armodafinil), sympathomimetic agents (methylphenidate, mixed amphetamine salts), dopamine and norepinephrine reuptake inhibitor (solriamfetol), and central nervous system depressant (sodium oxybate). All of these therapies have the potential for abuse and are controlled substances: methylphenidate (CII), amphetamine salts (CII), sodium oxybate (CIII), modafinil (CIV), armodafinil (CIV) and solriamfetol (CIV).

Modafinil has demonstrated effectiveness in treating daytime sleepiness due to narcolepsy at a recommended dose of 200 mg once daily.[1] Increases in MWT ranged from 8.1 to 8.9 minutes compared to 5.1 minutes for placebo ($p<0.05$) and changes in ESS score decreases were 13.0 to 14.4 versus placebo increase of 17 ($p<0.001$). There is no evidence to suggest that doses beyond 200 mg confer additional benefit.[7]

Armodafinil, is the R-enantiomer of modafinil, Changes in MWT from baseline to 12 weeks for armodafinil was an increase of 1.3, 2.6, and 1.9 minutes 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 comparisons).[7] A head-to-head comparison of both drugs showed similar efficacy in the treatment of excessive sleepiness due to sleep work disorder (SWD).[8]

Methylphenidate has had a long history of use in EDS with success in reducing sleepiness symptoms by inhibiting reuptake of dopamine and norepinephrine into presynaptic nerve terminals. However, doses required to obtain therapeutic levels and desired outcomes are correlated with an increased risk of adverse events, including abuse and dependence.[9] Methylphenidate is associated with more side effects compared to other EDS treatments, which include adverse cardiovascular events (i.e. hypertension, arrhythmias), psychoses, and diminished seizure threshold.[10]

Amphetamines such as mixed amphetamine salts (dextroamphetamine/amphetamine) and dextroamphetamine (Dexedrine) are also used as EDS agents, though typically considered second-line due to adverse effects and risk of abuse.[11] Amphetamine salts act primarily by promoting release of dopamine and norepinephrine from presynaptic nerve terminals. This drug class has a history of success and efficacy for EDS; however, high dose requirements promote development of significant adverse effects similar to methylphenidate (cardiovascular effects, psychoses, and dependency).[9]

Sodium oxybate, a GABA derivative that acts as an inhibitory chemical transmitter in the brain, approved by the Food and Drug Administration (FDA) for the treatment of EDS due to narcolepsy in patients aged 7 years and older. Sodium oxybate is currently available only through the Xyrem® REMS Program due to risk of central nervous system depression and potential for abuse/misuse.[12]

Concomitant use of modafinil with sodium oxybate has shown additive effects and subsequent improvement from baseline in EDS outcomes compared to sodium oxybate monotherapy or placebo: MWT +2.68, +0.58 , and -2.72 minutes, respectively ($p<0.001$ for combined therapy vs monotherapy and combined therapy vs placebo) and ESS -4.0, -3.0 and 0.0 minutes, respectively ($p<0.001$ for combined therapy vs monotherapy and combined therapy vs placebo).[13]

Solriamfetol was approved in 2019 and has demonstrated improved MWT and ESS compared to placebo for patients with OSA or narcolepsy.[14] Clinical trial data for solriamfetol for treatment of narcolepsy is displayed in **Table 1**. Similar efficacy was noted in patients with OSA. The currently FDA-approved maximum dose is 150 mg daily as higher doses were associated with no difference in efficacy and more frequent adverse events. There is insufficient evidence comparing solriamfetol to other therapies used in the treatment of EDS. Long-term safety and efficacy, in addition to mechanism of action, remain unclear.

Table 1. Efficacy of Solriamfetol Compared to Placebo in Narcolepsy[14]

Endpoint	Dose Strength	Mean Difference
Maintenance of Wakefulness Test (minutes)	150 mg daily	7.65 (95% CI, 3.99 to 11.31) p<0.0001
	75 mg daily	2.26 (95% CI, -1.04 to 6.28) p=0.1595
Epworth Sleepiness Scale (range 0-24)	150 mg daily	-3.8 (95% CI, -5.6 to -2.0) p<0.0001
	75 mg daily	-2.2 (95% CI, -4.0 to -0.3) p=0.0211

Abbreviations: CI = confidence interval

There is insufficient evidence for off-label use of other medications for the treatment symptoms related to EDS including selegiline, tricyclic antidepressants, and selective serotonin reuptake inhibitors.[1,13]

Adverse Events

The most common adverse events associated with EDS therapy include: headache, nausea, vomiting, diarrhea, insomnia, dizziness, anxiety, diminished appetite, weight loss, and tachycardia.[10,15-19] Armodafinil has a longer half-life compared to modafinil and a subsequent longer duration of action, which has been associated with a higher risk of developing adverse reactions. Though uncommon, use of modafinil or armodafinil can increase the risk of emergent psychiatric symptoms, including suicidal ideation, at any dose, and DRESS (drug reaction with eosinophilia and systemic symptoms), also known as multi-organ hypersensitivity.[7] Solriamfetol use was associated with increases in blood pressure and heart rate during clinical trials, and use in patients with uncontrolled blood pressure is not recommended.[19] Because patients with any acute, uncontrolled medical condition were excluded from clinical trials of solriamfetol, the risk of long-term cardiovascular events is unknown. Black box warnings exist for the following EDS treatments: sodium oxybate (central nervous system depression and misuse/abuse), methylphenidate (abuse and dependence), and mixed amphetamine salts (potential for abuse).[10,17,18]

Cost

Thirty-day cost comparisons of EDS treatments are detailed in **Table 2**. There is no established benefit of newer therapies that are associated with a much higher cost.

Table 2. Comparative Costs for EDS Treatments

Medication	Initial Dose	30-Day Supply Cost
Methylphenidate	5 mg twice daily	$3.59
Dextroamphetamine/ amphetamine	10 mg daily	$7.28
Modafinil	200 mg daily	$12.25
Armodafinil	150 mg daily	$16.20
Sodium oxybate (Xyrem®)	2.25 g twice daily	$9720
Solriamfetol (Sunosi™)	75 mg daily	$690

Oregon Health Authority Average Acquisition Costs (7/31/19) and drugs.com

EDS due to shift-work and unspecified hypersomnia are not funded by the Oregon Health Plan (OHA). Modafinil and armodafinil are available with prior authorization approval.

Conclusion

- There is insufficient comparative evidence for EDS treatments to inform strong conclusions on place in therapy.
- Newer EDS treatments are substantially more costly than established therapies.
- Careful differential diagnosis of sleep symptom origin is critical to safe and effective treatment of sleep disorders.

Peer Reviewed By: Tracy Klein, PhD, ARNP, Associate Professor WSU Vancouver, Abby Frye, Pharm D, BCACP, Clinical Pharmacy Specialist, Primary Care Providence Medical Group

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Drug Class Literature Scan: Substance Use Disorders, Opioid and Alcohol

Date of Review: November 2019

Date of Last Review: January 2019
Literature Search: 01/01/2018–06/20/2019

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

Conclusions:

- Since the last class update on drugs used to manage substance use disorders (SUDs), two new systematic reviews were published and 2 new buprenorphine/naloxone formulations received FDA approval.
- The Canadian Agency for Drugs and Technologies in Health (CADTH) issued a Rapid Response Report in April 2019 focused on recently published evidence for the use of buprenorphine in management of opioid use disorder (OUD).[1] Although there were some instances where specific formulations of buprenorphine demonstrated statistically significant improvements in outcomes of interest (e.g., reduction in opioid consumption, prevention of relapse, maintenance of abstinence, and retention into treatment) compared to other formulations, no clear patterns emerged regarding the comparative clinical effectiveness of buprenorphine for the treatment of OUD.[1] With respect to the safety of various formulations, none of the included studies reported statistically significant differences in the safety profiles of buprenorphine formulations.[1]
- In May 2019, CADTH published a report evaluating the use of buprenorphine for management of OUD during pregnancy.[2] The report identified a lack of evidence regarding the comparative effectiveness and safety of various buprenorphine or buprenorphine-naloxone formulations for the treatment of opioid use disorders during pregnancy.[2]

Recommendations:

- Based on the review of recently published evidence, no changes to the preferred drug list (PDL) or prior authorization (PA) criteria are recommended.

Summary of Prior Reviews and Current Policy

A class update focused on drugs used to manage substance use disorders (SUDs) was presented to the Pharmacy and Therapeutics (P and T) Committee in January 2019. Current guidelines from the Veterans Administration and Department of Defense primarily recommend utilization of methadone (in the context of a treatment program), or buprenorphine/naloxone for patients with OUD (strong recommendation).[3] Buprenorphine alone may be considered for patients who are pregnant (weak recommendation), and extended-release injectable naloxone is recommended as an option for patients for whom opioid agonist therapy is contraindicated, unacceptable, or unavailable, and who have established opioid abstinence for at least 7 days without acute withdrawal symptoms (strong recommendation).[3] Two unique therapies were included in the January 2019 class update. In November 2017, the FDA approved buprenorphine extended-release injection (Sublocade™) to treat patients with moderate-to-severe OUD who have first received treatment with a transmucosal buprenorphine-containing product for at least 7 days.[4] In May 2018, lofexidine (Lucemyra™) received FDA approval for short-term (up to 14 days) mitigation of severe opioid withdrawal

symptoms in adults to facilitate abrupt opioid discontinuation.[5] Lofexidine, a centrally acting alpha2-adrenergic receptor agonist, is structurally and pharmacologically similar to clonidine.[5] There is poor quality evidence from one published trial that adults undergoing acute withdrawal from opioids or heroin experienced less symptoms with lofexidine compared to placebo as assessed by the mean Short Opioid Withdrawal Scale (SOWS)-Gossop on day 3 of treatment.[6] After reviewing the class update, the P and T committee recommended the following:

- Make lofexidine non-preferred on the Prioritized Drug List (PDL) and implement PA criteria to ensure appropriate utilization.
- Add extended release subcutaneous buprenorphine injection (Sublocade™) to PA criteria for buprenorphine and buprenorphine/naloxone products.

In January 2017, in order to minimize barriers to care and provide increased access to medications for the treatment of OUD, the P and T Committee recommended removal of PA criteria for naltrexone extended release injection and preferred buprenorphine/naloxone sublingual tablets and film (unless the daily dose of buprenorphine exceeds 24 mg). At the January 2019 P and T Committee meeting, a policy evaluation assessing the impact of removing prior authorization (PA) requirements for preferred MAT for treatment of OUD was also presented. It was reported that utilization of buprenorphine/naloxone and medical claims for MAT continue to increase. After removal of the PA criteria in January 2017, approximately 83% of patients prescribed MAT had an initial paid claim compared to 40% of patients in the year prior to the PA removal. Off-label use of MAT appears to be limited. Approximately 85% of patients had a diagnosis of OUD based on available diagnoses or presence of medical claims for OUD. Utilization of non-pharmacological psychosocial support or enrollment in SUD treatment programs was limited. Only 39-40% of patients had at least one claim for non-pharmacological substance use disorder (SUD) services, and approximately 34% of patients had long-term utilization of non-pharmacological therapy after 3 months of treatment with MAT.

In the Oregon Health Plan (OHP) Fee-For-Service (FFS) program, preferred agents on the Preferred Drug List (PDL) include: buprenorphine/naloxone film and sublingual tablets, acamprosate tablets, naltrexone extended-release injection, and naltrexone tablets. **Appendix 1** lists the current PDL status for medications used in treatment of SUD. Buprenorphine sublingual tablets are restricted for use in pregnant females and all buprenorphine monotherapy products require PA as outlined in the clinical PA criteria listed in **Appendix 6**. In the second quarter of 2019 (May through September 2019), 75% of OHP FFS claims for SUD medications were for buprenorphine/naloxone, 13% of claims were for naltrexone, 11% of claims were for buprenorphine, and 1% of claims were for acamprosate.

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:

Buprenorphine for Management of Opioid Use Disorder

The Canadian Agency for Drugs and Technologies in Health issued a Rapid Response Report in April 2019 focused on recently published evidence for the use of buprenorphine in management of OUD.[1] Several formulations of buprenorphine are available for the treatment of OUD in Canada, including the single ingredient buccal film, buprenorphine extended-release injection, subcutaneous implant, as well as the combination product of buprenorphine with naloxone in a sublingual tablet. The CADTH search was limited to English-language documents published between January 1, 2014 and March 20, 2019. Two systematic reviews and 3 RCTs were identified regarding the clinical effectiveness and safety of various buprenorphine formulations for the treatment of OUD.[1] A primary limitation of the RCTs was that participants and outcome assessors were not blinded to the treatment recieved.[1] Given that several of the outcomes reported in these trials were based on subjective measures (e.g., Subjective Opiate Withdrawal Scale [SOWS] scores, opioid craving visual analogue scale scores, or self-reported use of heroin), the findings of open-label studies may be at risk for bias in either direction depending on the perceptions and expectations of participants and clinicians involved.[1] Though there were some instances where specific formulations of buprenorphine demonstrated statistically significant improvements in outcomes of interest (e.g., reduction in opioid consumption, prevention of relapse, maintenance of abstinence, and retention into treatment) compared to other formulations, no clear patterns emerged regarding the comparative clinical effectiveness of buprenorphine for the treatment of OUD.[1] With respect to the safety of various formulations, none of the included studies reported statistically significant differences in the safety profiles of buprenorphine formulations.[1]

Buprenorphine for Opioid Use Disorders during Pregnancy

In May 2019, CADTH published a report evaluating the use of buprenorphine for management of OUD during pregnancy.[2] The search was limited to English language documents published between January 1, 2014 and April 8, 2019. Three evidence based guidelines met the inclusion-criteria and were included in the report.[2] One guideline was from the British Columbia Ministry of Health, one from the Society of Obstetricians and Gynecologists of Canada, and one from the World Health Organization (WHO).[2] The included guidelines were also supported by evidence of limited quantity and quality.[2] The report identified a lack of evidence regarding the comparative effectiveness, safety, and cost-effectiveness of various buprenorphine or buprenorphine-naloxone formulations for the treatment of opioid use disorders during pregnancy.[2] Two of three guidelines contained relevant recommendations that reflected this lack of high-quality comparative evidence.[2] These two guidelines recommended buprenorphine treatment in preference to the buprenorphine-naloxone formulation for opioid use disorders during pregnancy.[2] One other Canadian guideline cited the same evidence to support the use of buprenorphine-naloxone as a safe and effective alternative to buprenorphine alone during pregnancy.[2] No additional recommendations for various buprenorphine or buprenorphine-naloxone formulations during pregnancy were identified.

After review, 1 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).[7]

New Guidelines: No new guidelines were identified.

New Formulations:

Cassipa® a new dosage strength of buprenorphine/naloxone (16mg/4mg) sublingual film received Food and Drug Administration (FDA) approval September 2018. The drug is indicated for maintenance treatment of opioid dependence and was approved through an abbreviated approval pathway based on previous evidence for buprenorphine/naloxone safety and efficacy.

Brixadi™, an extended-release formulation of buprenorphine for subcutaneous administration weekly and monthly received tentative FDA approval December 2018. It is indicated for the treatment of moderate-severe OUD in patients who have initiated treatment with a single dose of a transmucosal buprenorphine product or who are already being treated with buprenorphine. The FDA provided tentative approval pending patent considerations (potential market entry in 2020). The drug must be administered only by healthcare providers in a healthcare setting.

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

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Formulation	PDL
acamprosate calcium	ACAMPROSATE CALCIUM	ORAL	TABLET DR	Y
buprenorphine HCl/naloxone HCl	BUPRENORPHINE-NALOXONE	SUBLINGUAL	FILM	Y
buprenorphine HCl/naloxone HCl	SUBOXONE	SUBLINGUAL	FILM	Y
buprenorphine HCl/naloxone HCl	BUPRENORPHINE-NALOXONE	SUBLINGUAL	TAB SUBL	Y
buprenorphine HCl/naloxone HCl	ZUBSOLV	SUBLINGUAL	TAB SUBL	Y
naltrexone HCl	DEPADE	ORAL	TABLET	Y
naltrexone HCl	NALTREXONE HCL	ORAL	TABLET	Y
naltrexone HCl	REVIA	ORAL	TABLET	Y
naltrexone microspheres	VIVITROL	INTRAMUSC	SUS ER REC	Y
buprenorphine	SUBLOCADE	SUB-Q	SOLER SYR	N
buprenorphine HCl	BUPRENORPHINE HCL	SUBLINGUAL	TAB SUBL	N
buprenorphine HCl/naloxone HCl	BUNAVAIL	BUCCAL	FILM	N
disulfiram	ANTABUSE	ORAL	TABLET	N
disulfiram	DISULFIRAM	ORAL	TABLET	N
lofexidine HCl	LUCEMYRA	ORAL	TABLET	N
buprenorphine HCl	PROBUPHINE	IMPLANT	IMPLANT	

Appendix 2: New Comparative Clinical Trials

A total of 30 citations were manually reviewed from the initial literature search. After further review, 27 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 3 trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

<table>
<tr><th>Study</th><th>Comparison</th><th>Population</th><th>Primary Outcome</th><th>Results</th></tr>
<tr>
<td>Bisaga, et al[8]

DB, MC, RCT

N=378
19 sites
7 days</td>
<td>PO NTX + SL BUP
Vs.
PO NTX + PBO
Vs.
PBO

To determine the efficacy, of oral NTX used in with BUP prior to the first dose of XR-NTX for detoxification.</td>
<td>-Patients aged 18-60 yo with diagnosis of OUD
-Use of opioids > 3 mos
-Mild withdrawal (COWS ≥6)</td>
<td>Proportion of patients who received and tolerated an XR-NTX injection, as demonstrated by COWS score ≤12 or SOWS score ≤10 one hour following XR-NTX administration.</td>
<td>
<table>
<tr><th>Outcome</th><th>NTX/BUP (n=124)</th><th>NTX/PBO (n=126)</th><th>PBO (n=124)</th></tr>
<tr><td>Received XR-NTX (%)</td><td>46.8%</td><td>40.5%</td><td>46.8%</td></tr>
<tr><td>Received and tolerated XR-NTX</td><td>N = 57 (46%)</td><td>N=51 (40.5%)</td><td>N=57 (46%)</td></tr>
<tr><td>P value</td><td>0.94</td><td>0.383</td><td>N/A</td></tr>
</table>
A 7-day detoxification protocol with NTX alone or NTX with BUP provided similar rates of induction onto XR-NTX as placebo (no differences).
</td>
</tr>
<tr>
<td>Lofwall, et al[9]

DB, NI, MC, RCT

N=428
35 sites
24 weeks</td>
<td>SC BUP + SL PBO
Vs.
SL BUP-NX + SC PBO

To determine whether treatment with weekly and monthly SC BUP depot formulations is noninferior to a daily SL BUP-NX in treatment of OUD.</td>
<td>Patients aged 18-65 yo with moderate-to-severe OUD</td>
<td>Mean percentage of urine samples with test results negative for illicit opioids for weeks 1 to 24 and percent of responders.</td>
<td>Table 2.
<table>
<tr><th>Outcome</th><th>SL BUP-NX</th><th>SC-BUP</th><th>Treatment differences</th></tr>
<tr><td>Opioid negative urine sample</td><td>28.4 (2.5%)</td><td>35.1 (2.5%)</td><td>6.7 (95% CI: -0.1 to 13.6) P<0.001 for NI</td></tr>
<tr><td>% of responders</td><td>31 (14.4%)</td><td>37.0 (17.4%)</td><td>3.0 (95% CI: -4.0 to 9.9) P<0.001 for NI</td></tr>
</table>
Compared with SL buprenorphine, depot buprenorphine was noninferior for both primary outcomes.
</td>
</tr>
<tr>
<td>Sullivan, et al.[10]

OL, PG, RCT

N=60
24 weeks</td>
<td>PO NTX
Vs.
IM XR-NTX

Compare the outcomes of patients with OUD treated with XR-NTX or oral NTX</td>
<td>Patients aged 18-60 yo with opioid dependence</td>
<td>The primary aim of this study was to compare the retention (time to dropout) of participants across the two treatment arms during 24 weeks of treatment</td>
<td>
<table>
<tr><td>Outcome</td><td>XR-NTX N=28</td><td>PO NTX N=32</td><td>P value</td></tr>
<tr><td>Treatment retention</td><td>N=16 (57.1%)</td><td>N=9 (28.1%)</td><td>HR=2.19 95% CI = 1.07 to 4.43</td></tr>
</table>
Patients receiving XR-naltrexone had twice the rate of treatment retention at 6 months compared with those taking oral naltrexone.
</td>
</tr>
</table>

Abbreviations: BUP=buprenorphine; COWS=Clinical Opiate Withdrawal Scale; DB=double blind; HR=hazard ratio; IM=intramuscular; MC=multicenter; Mos=months; NI=non-inferiority; NTX=oral naltrexone; NX=naloxone; OL=open label; OUD=opioid use disorder; PBO=placebo; PG=parallel group; PO=oral; RCT=randomized clinical trial; SC=subcutaneous; SL=sublingual; SOWS=Subjective Opiate Withdrawal Scale; XR-NTX=extended-release naltrexone; YO=years old

Appendix 3: Abstracts of Comparative Clinical Trials

1**. Outpatient transition to extended-release injectable naltrexone for patients with opioid use disorder: A phase 3 randomized trial.**[8]

BACKGROUND:
Injectable extended-release naltrexone (XR-NTX), approved to prevent relapse to opioid dependence, requires initial abstinence. This multisite outpatient clinical trial examined the efficacy and safety of low-dose oral naltrexone (NTX), combined with a brief buprenorphine (BUP) taper and standing ancillary medications, for detoxification and induction onto XR-NTX.
METHODS:
Patients (N = 378) were randomized, stratified by primary short-acting opioid-of-use, to one of three regimens: NTX + BUP; NTX + placebo BUP (PBO-B); placebo NTX (PBO-N) + PBO-B. Patients received 7 days of ascending NTX or placebo, concurrent with a 3-day BUP or placebo taper, and ancillary medications in an outpatient setting. Daily psychoeducational counseling was provided. On Day 8, patients passing a naloxone challenge received XR-NTX.
RESULTS:
Rates of transition to XR-NTX were comparable across groups: NTX/BUP (46.0%) vs. NTX/PBO-B (40.5%) vs. PBO-N/PBO-B (46.0%). Thus, the study did not meet its primary endpoint. Adverse events, reported by 32.5% of all patients, were mild to moderate in severity and consistent with opioid withdrawal. A first, second, and third XR-NTX injection was received by 44.4%, 29.9%, and 22.5% of patients, respectively. Compared with the PBO-N/PBO-B group, the NTX/BUP group demonstrated higher opioid abstinence during the transition and lower post-XR-NTX subjective opioid withdrawal scores.
CONCLUSIONS:
A 7-day detoxification protocol with NTX alone or NTX + BUP provided similar rates of induction to XR-NTX as placebo. For those inducted onto XR-NTX, management of opioid withdrawal symptoms prior to induction was achieved in a structured outpatient setting using a well-tolerated, fixed-dose ancillary medication regimen common to all three groups.

2. **Weekly and Monthly Subcutaneous Buprenorphine Depot Formulations vs Daily Sublingual Buprenorphine with Naloxone for Treatment of Opioid Use Disorder: A Randomized Clinical Trial**.[9]

OBJECTIVE:
To determine whether treatment involving novel weekly and monthly subcutaneous (SC) buprenorphine depot formulations is noninferior to a daily sublingual (SL) combination of buprenorphine hydrochloride and naloxone hydrochloride in the treatment of opioid use disorder.
DESIGN, SETTING, AND PARTICIPANTS:
This outpatient, double-blind, double-dummy randomized clinical trial was conducted at 35 sites in the United States from December 29, 2015, through October 19, 2016. Participants were treatment-seeking adults with moderate-to-severe opioid use disorder.
INTERVENTIONS:
Randomization to daily SL placebo and weekly (first 12 weeks; phase 1) and monthly (last 12 weeks; phase 2) SC buprenorphine (SC-BPN group) or to daily SL buprenorphine with naloxone (24 weeks) with matched weekly and monthly SC placebo injections (SL-BPN/NX group).
MAIN OUTCOMES AND MEASURES:
Primary end points tested for noninferiority were response rate (10% margin) and the mean proportion of opioid-negative urine samples for 24 weeks (11% margin). Responder status was defined as having no evidence of illicit opioid use for at least 8 of 10 prespecified points during weeks 9 to 24, with 2 of these at week 12 and during month 6 (weeks 21-24). The mean proportion of samples with no evidence of illicit opioid use (weeks 4-24) evaluated by a cumulative distribution function (CDF) was an a priori secondary outcome with planned superiority testing if the response rate demonstrated noninferiority.

RESULTS:
A total of 428 participants (263 men [61.4%] and 165 women [38.6%]; mean [SD] age, 38.4 [11.0] years) were randomized to the SL-BPN/NX group (n = 215) or the SC-BPN group (n = 213). The response rates were 31 of 215 (14.4%) for the SL-BPN/NX group and 37 of 213 (17.4%) for the SC-BPN group, a 3.0% difference (95% CI, -4.0% to 9.9%; P < .001). The proportion of opioid-negative urine samples was 1099 of 3870 (28.4%) for the SL-BPN/NX group and 1347 of 3834 (35.1%) for the SC-BPN group, a 6.7% difference (95% CI, -0.1% to 13.6%; P < .001). The CDF for the SC-BPN group (26.7%) was statistically superior to the CDF for the SL-BPN/NX group (0; P = .004). Injection site adverse events (none severe) occurred in 48 participants (22.3%) in the SL-BPN/NX group and 40 (18.8%) in the SC-BPN group.
CONCLUSIONS AND RELEVANCE:
Compared with SL buprenorphine, depot buprenorphine did not result in an inferior likelihood of being a responder or having urine test results negative for opioids and produced superior results on the CDF of no illicit opioid use. These data suggest that depot buprenorphine is efficacious and may have advantages.

3. **A Randomized Trial Comparing Extended-Release Injectable Suspension and Oral Naltrexone, Both Combined With Behavioral Therapy, for the Treatment of Opioid Use Disorder**.[10]
OBJECTIVE:
The oral formulation of the opioid antagonist naltrexone has shown limited effectiveness for treatment of opioid use disorder due to poor adherence. Long-acting injection naltrexone (XR-naltrexone), administered monthly, circumvents the need for daily pill taking, potentially improving adherence, and has been shown to be superior to placebo in reducing opioid use over 6 months of treatment. This open-label trial compared the outcomes of patients with opioid use disorder treated with XR-naltrexone or oral naltrexone in combination with behavioral therapy.
METHOD:
Sixty opioid-dependent adults completed inpatient opioid withdrawal and were transitioned to oral naltrexone. They were stratified by severity of opioid use (six or fewer bags versus more than six bags of heroin per day) and randomly assigned (1:1) to continue treatment with oral naltrexone (N=32) or XR-naltrexone (N=28) for 24 weeks. The first dose of XR-naltrexone (380 mg) was administered prior to discharge, with monthly doses thereafter, and oral naltrexone was given in a 50-mg daily dose. All participants received weekly behavioral therapy to support treatment and adherence to naltrexone.
RESULTS:
A Cox proportional hazards model adjusting for race, gender, route of use, and baseline opioid use severity indicated that significantly more patients were retained in treatment for 6 months in the XR-naltrexone group (16 of 28 patients, 57.1%) than in the oral naltrexone group (nine of 32 patients, 28.1%) (hazard ratio=2.18, 95% CI=1.07, 4.43).
CONCLUSIONS:
Patients receiving XR-naltrexone had twice the rate of treatment retention at 6 months compared with those taking oral naltrexone. These results support the use of XR-naltrexone combined with behavioral therapy as an effective treatment for patients seeking opioid withdrawal and nonagonist treatment for preventing relapse to opioid use disorder.

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to June Week 3 2019 Ovid MEDLINE(R) In-Process & Other Non-Indexed Citation June 20, 2019

1 exp Buprenorphine/	3591
2 exp Buprenorphine, Naloxone Drug Combination	217
3 exp Naltrexone/	4693
4 Lofexidine.mp	103
5 Substance-Related Disorders	51433
6 1 or 2 or 3 or 4	8251
7 6 and 5	374

8 limit 5 to (English language and humans and yr="2018 -Current" and (clinical trial, all or clinical trial or comparative study or controlled clinical trial or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 7

Ovid MEDLINE(R) without Revisions 1996 to June Week 3 2019; Ovid MEDLINE(R) In-Process & Other Non-Indexed Citation June 20, 2019

1 acamprosate.mp.	768
2 exp Disulfiram/	3405
3 exp Naltrexone/	7577
4 exp Alcoholism/	73266
5 exp Substance-Related Disorders/	266719
6 exp Alcohol Deterrents/	11669
7 1 or 2 or 3	11331
8 4 or 5 or 6	274338
9 7 and 8	11308

10 limit 9 to (English language and humans and yr="2018 -Current" and (clinical trial, all or clinical trial or comparative study or controlled clinical trial or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 23

Appendix 5: Key Inclusion Criteria

Population	Patients with opioid or alcohol use disorder
Intervention	Various formulations of buprenorphine (e.g., extended-release subcutaneous injection, sublingual, implant, transdermal, intramuscular) or buprenorphine-naloxone combinations or naltrexone
Comparator	Various formulations of buprenorphine (e.g., extended-release subcutaneous injection, sublingual, implant, transdermal, intramuscular) or buprenorphine-naloxone combinations or naloxone
Outcomes	1. Clinical effectiveness (e.g., reduction in opioid consumption, prevention of relapse, maintenance of abstinence, retention into treatment, and adherence to medication.) 2. Safety (e.g., reduction in misuse and diversion, reports or evidence of abuse, urine drug screening results, overdose, all-cause mortality)
Timing	Up to 24 weeks
Setting	Outpatient

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Policy Proposal: Substance Use Disorder

Purpose:
The purpose of this policy proposal is to update current prior authorization (PA) criteria to comply with new legislation.

Background:
During the 2019 legislative session, the Oregon legislature passed House Bill 2257 which declared the legislative intent to consider substance use disorder as a chronic illness.[1] The new legislation requires the Oregon Health Authority to prohibit use of prior authorization (PA) during the first 30 days of medication-assisted treatment for both opioid- and alcohol-related substance use disorders.[1] This update recommends changes to PA and preferred drug list (PDL) status to comply with this new legislation and proposes a retrospective drug use review (DUR) program with the goals of avoiding interruptions in therapy and ensuring appropriate use of long-term second-line treatment options for opioid use disorder (OUD).

Currently in fee-for-service Medicaid, treatments for OUD or alcohol use disorder available without PA include acamprosate tablets, naltrexone tablets, naltrexone extended release injection, and preferred buprenorphine/naloxone sublingual tablets and film (unless the daily dose of buprenorphine exceeds 24 mg to prevent off-label use for treatment of pain). Drug therapy for OUD or alcohol use disorder which are currently non-preferred and require PA include Bunavail® (buprenorphine/naloxone film), buprenorphine sublingual tablets, buprenorphine extended-release injection, buprenorphine implants, disulfram and lofexidine. Methadone for the treatment of OUD is required to be dispensed by a practitioner rather than dispensed through a pharmacy and is not subject to PA. The intent of the current PA criteria is to limit off-label use for pain, encourage use of monotherapy products for appropriate patients, and prevent concomitant opioid prescribing. In a previous policy evaluation of therapies for OUD, about 14% of patients prescribed OUD treatment had no diagnosis of opioid use, dependence or abuse based on claims history.

Recent high quality guidelines from the Veterans Affairs/Department of Defense (VA/DOD) recommend use of buprenorphine-naloxone or methadone as first-line treatment options for OUD (strong recommendation based on high quality evidence).[2] Similar recommendations were made in a high quality guideline from the Canadian Research Initiative in Substance Misuse published in 2018 recommending buprenorphine/naloxone as first-line therapy and methadone as a second-line option.[3] Buprenorphine monotherapy is recommended only in patients who are pregnant.[2] Current evidence indicates that, while oral buprenorphine monotherapy has similar efficacy to combination buprenorphine/naloxone, it is associated with a significantly higher rate of abuse, misuse, and diversion compared to combination buprenorphine-naloxone products.[4] Extended-release injectable naloxone may be considered as a treatment option for patients for whom buprenorphine/naloxone or methadone is contraindicated, unacceptable, or unavailable, and who have established opioid abstinence for at least 7 to 10 days based on moderate quality evidence.[2]

For treatment of alcohol use disorder, 2015 guidelines from the VA/DOD recommend choice of treatment with either acamprosate, disulfiram, naltrexone (oral or extended-release injection) or topiramate be based on individual risks/benefit assessment, specific needs, and patient preferences (strong recommendation).[2] There is insufficient evidence to recommend one agent over another, and in all cases, psychosocial interventions are recommended to successfully improve outcomes, decrease alcohol use, and improve abstinence in patients with alcohol use disorder (strong recommendation based on moderate quality evidence).[2]

Examples of psychosocial interventions may include behavioral couples counseling, cognitive behavioral therapy, 12-step programs, or motivational enhancement therapy.

In an evaluation of paid and denied claims for substance use disorder from 1/1/2019 to 3/31/2019, there were 632 patients prescribed therapies for OUD or alcohol use disorder. Patients may be counted more than once if they were prescribed multiple types of therapy. About 77% of prescribed therapy was for preferred products and 23% was for non-preferred products. All but one request for preferred therapy was initially paid or paid within 30 days of the request, indicating very little utilization of high dose buprenorphine (>24 mg/day) for preferred products. Doses exceeded 24mg per day in about 4% of members with denied claims for non-preferred buprenorphine monotherapy (n=7). The most commonly requested non-preferred product was oral buprenorphine monotherapy. Forty-four percent of patients requesting buprenorphine monotherapy (n=56) had a subsequent PA approved and 11% of patients (n=14) switched to a preferred agent. In 45% of patients with an initial denied claim, there were no paid claims for subsequent therapy. Of the patients with no subsequent paid fee-for-service claims for OUD, 92% were subsequently enrolled in a coordinated care organization, lost Medicaid eligibility, or had other insurance which may have paid for their therapy. Three patients had a PA approved but no subsequent paid claims for the therapy.

Recommendations:

- Designate products as either preferred or voluntary non-preferred based on evaluation of costs in executive session.
- Recommend removal of PA requirement for all OUD products except if dose limit of 24 mg buprenorphine per day is exceeded for transmucosal products (**Appendix 1**).
- Continue to monitor use of substance use disorder products to assess potential changes in medically appropriate use.

References:

1. House Bill 2257 (enrolled). 80th Oregon Legislative Assembly - 2019 Regular session. Available at https://olis.leg.state.or.us/liz/2019R1/Downloads/MeasureDocument/HB2257. Accessed 9/17/19.
2. Clinical Practice Guideline for Substance Use Disorders (2015). U.S. Department of Veterans Affairs/Department of Defense. http://www.healthquality.va.gov/guidelines/MH/sud/VADoDSUDCPGRevised22216.pdf. Accessed September 19, 2019.
3. Bruneau J, Ahamad K, Goyer ME, et al. Management of opioid use disorders: a national clinical practice guideline. *Canadian Medical Association journal.* 2018;190(9):E247-e257.
4. Canadian Agency for Drugs and Technologies in Health. Buprenorphine formulations for the treatment of opioid use disorders: a review of comparative clinical effectiveness, cost-effectiveness and guidelines. Ottawa: 2017 Jul. (CADTH rapid response report: summary with critical appraisal). https://www.cadth.ca/sites/default/files/pdf/htis/2017/RC0908%20Buprenorphine%20Formulations%20Final.pdf.

Appendix 1. Proposed Prior Authorization Criteria

Buprenorphine and Buprenorphine/Naloxone

Goals:

- Prevent use of high-dose oral buprenorphine products for off-label indications.
  ~~Encourage use of buprenorphine products on the Preferred Drug List.~~
- ~~Restrict use of buprenorphine products under this PA to management of opioid use disorder.~~
- ~~Restrict use of oral transmucosal buprenorphine monotherapy products (without naloxone) to pregnant patients or females actively trying to conceive.~~

Length of Authorization:

- Up to 6 months

Requires PA:

- ~~Buprenorphine sublingual tablets~~
- ~~Suboxone® and generics (~~Transmucosal buprenorphine~~/naloxone) film and sublingual tablets~~ products that exceed an average daily dose of 24 mg per day ~~of buprenorphine~~
- ~~Bunavail® (buprenorphine/naloxone buccal film)~~
- ~~Zubsolv® (buprenorphine/naloxone sublingual tablets)~~
- ~~Probuphine® (buprenorphine subdermal implants)~~
- ~~Sublocade™ (buprenorphine extended-release subcutaneous injection)~~

Covered Alternatives:

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

Approval Criteria		
1. Is the diagnosis funded by the OHP?	**Yes:** Go to #2	**No:** Pass to RPh. Deny; not funded by OHP
~~Is the request for renewal of therapy previously approved by the FFS system?~~	~~**Yes:** Go to **Renewal Criteria**~~	~~**No:** Go to #3~~

Approval Criteria		
2. Is the prescription for opioid use disorder (opioid dependence or addiction)?	**Yes:** Go to #34	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the prescription for a transmucosal formulation of buprenorphine (film, tablet) with an average daily dose of more than 24 mg (e.g., >24 mg/day or >48 mg every other day)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #4
~~Is the patient part of a comprehensive treatment program for substance abuse that includes psychosocial support system (e.g. individual and group counseling, intensive outpatient treatment, recovery support services, or 12-step fellowship)?~~	~~**Yes:** Go to #5~~	~~**No:** Pass to RPh. Deny; medical appropriateness.~~ ~~Buprenorphine therapy must be part of a comprehensive treatment program that includes psychosocial support.~~
~~Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com), evaluated the PDMP at least once in the past 6 months, and verified that the patient is not currently t prescribed any opioid analgesics from other prescribers?~~	~~**Yes:** Go to #6~~	~~**No:** Pass to RPh. Deny; medical appropriateness~~
~~3.~~4. Is the requested medication a preferred agent?	**Yes:** ~~Go to #8~~ Approve for anticipated length of treatment or 6 months, whichever is less. Note: Notify prescriber concomitant naloxone is recommended if not present in claims history.	**No:** Go to #5~~7~~

Approval Criteria		
~~4.~~5. Will the prescriber switch to a preferred product? Note: Preferred products are reviewed for comparative safety and efficacy by the Oregon Pharmacy and Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** ~~Go to #8~~ Approve for anticipated length of treatment or 6 months, whichever is less. Note: Notify prescriber concomitant naloxone is recommended if not present in claims history.
~~Is the request for the buprenorphine implant system (Probuphine)?~~	~~**Yes:** Go to #9~~	~~**No:** Go to #10~~
~~5. Has the patient been *clinically stable* on 8 mg daily or less of Suboxone or Subutex (or equivalent, see Table 1) for at least 6 months?~~ ~~Note: see Table 1 for definition of clinical stability and for equivalent dosing of other buprenorphine products.~~	~~**Yes:** If all criteria in Table 1 met, approve 4 implants for 6 months.~~ ~~Note: Notify prescriber concomitant naloxone is recommended if not present in claims history.~~	~~**No:** Pass to RPh. Deny; medical appropriateness~~
~~Is the request for extended-release subcutaneous buprenorphine injection (Sublocade™)?~~	~~**Yes:** Go to #11~~	~~**No:** Go to # 13~~

Approval Criteria		
~~Is the provider registered through the Sublocade™ REMS program?~~ ~~Note: Sublocade carries a boxed warning that stipulates healthcare settings and pharmacies that order and dispense Sublocade™ must be certified in the Sublocade™ REMS program and comply with the REMS requirements due to serious harm or death if this product is administered intravenously. Prescriber offices that only order Sublocade from a certified pharmacy for a specific patient are exempt from certification. Further information is available at www.SublocadeREMS.com or call 1-866-258-3905.~~	~~**Yes:** Go to #12~~	~~**No:** Pass to RPh. Deny; medical appropriateness.~~
~~6. Has the patient been clinically stable on a transmucosal buprenorphine-containing product at a dose of 8 to 24 buprenorphine per day (or equivalent-see note below) for a minimum of 7 days?~~ ~~Note: One Suboxone® (buprenorphine and naloxone) 8 mg/2 mg sublingual tablet provides equivalent buprenorphine exposure to one Subutex® (buprenorphine HCl) 8 mg sublingual tablet or one Bunavail® (buprenorphine and naloxone) 4.2mg/0.7 mg buccal film or one Zubsolv® (buprenorphine and naloxone) 5.7 mg/1.4 mg sublingual tablet~~ ~~Note: Notify prescriber concomitant naloxone is recommended if not present in claims history.~~	~~**Yes:** Approve 300mg once a month for 2 months followed by 100mg once a month for 6 months total~~ ~~Increasing the maintenance dose to 300mg once a month may be considered for patients who tolerate the 100mg dose but do not demonstrate a satisfactory clinical response as evidenced by self-reported illicit opioid use or urine drug screens positive for illicit opioid use.~~	~~**No:** Pass to RPh. Deny; medical appropriateness.~~
~~Is the prescription for a transmucosal formulation of buprenorphine (film, tablet) with an average daily dose of more than 24 mg (e.g., >24 mg/day or >48 mg every other day)?~~	~~**Yes:** Pass to RPh. Deny; medical appropriateness~~	~~**No:** Go to #14~~

Approval Criteria		
Is the prescribed product a buprenorphine monotherapy product (i.e., without naloxone)	**Yes:** Go to #15	**No:** Go to #17
Is the patient pregnant or a female actively trying to conceive?	**Yes:** Go to #17	**No:** Go to #16
Does the patient have a contraindication or intolerance to buprenorphine/naloxone combination products that prevents successful management of opioid use disorder?	**Yes:** Go to #17	**No:** Pass to RPh. Deny; medical appropriateness
What is the expected length of treatment?	Document length of therapy: _____ Approve for anticipated length of treatment or 6 months, whichever is shorter. Note: Notify prescriber concomitant naloxone is recommended if not present in claims history.	

Renewal Criteria		
1. Has the patient been assessed for the effectiveness of the treatment plan and overall progress that warrants continued treatment with buprenorphine?	**Yes:** Go to # 2.	**No:** Pass to RPh. Deny; medical appropriateness
2. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com), and has the prescriber verified evaluated the PDMP at least once in the past 6 months, and verified that the patient is not currently has not been prescribed any opioid analgesics from other prescribers?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Does the patient have a contraindication or intolerance to buprenorphine/naloxone combination products that prevents successful management of opioid use disorder?	**Yes:** Go to # 4	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria	
4. What is the expected length of treatment?	Document length of therapy: _____ Approve for anticipated length of treatment or 6 months, whichever is shorter. Note: Notify prescriber concomitant naloxone is recommended if not present in claims history.

Table 1. Criteria for Approved Use of Probuphine (buprenorphine implant).[1]

PROBUPHINE implants are only for use in patients who meet ALL of the following criteria:
• Patients should not be tapered to a lower dose for the sole purpose of transitioning to PROBUPHINE • Stable transmucosal buprenorphine dose (of 8 mg per day or less of a sublingual Subutex or Suboxone sublingual tablet or its transmucosal buprenorphine product equivalent) for 3 months or longer without any need for supplemental dosing or adjustments: ○ Examples of acceptable daily doses of transmucosal buprenorphine include: ▪ Subutex (buprenorphine) sublingual tablet (generic equivalent) 8 mg or less ▪ Suboxone (buprenorphine and naloxone) sublingual tablet (generic equivalent) 8 mg/2 mg or less ▪ Bunavail (buprenorphine and naloxone) buccal film 4.2 mg/0.7 mg or less ▪ Zubsolv (buprenorphine and naloxone) sublingual tablets 5.7 mg/1.4 mg or less
Consider the following factors in determining clinical stability and suitability for PROBUPHINE treatment: • no reported illicit opioid use • low to no desire/need to use illicit opioids • no reports of significant withdrawal symptoms • stable living environment • participation in a structured activity/job that contributes to the community • consistent participation in recommended cognitive behavioral therapy/peer support program • stability of living environment • participation in a structured activity/job
Reference: PROBUPHINE (buprenorphine implant for subdermal administration) [Prescribing Information]. Princeton, MJ: Braeburn Pharmaceuticals, Inc., May 2016.

P&T/DUR Review: *1/19 (DM); 1/17; 9/16; 1/15; 9/09; 5/09*
Implementation: *3/1/2019; 4/1/2017; 9/1/13; 1/1/10*

Lofexidine

Goal(s):

- Encourage use of substance use disorder medications on the Preferred Drug List.

- Restrict use of lofexidine under this PA to ensure medically appropriate use of lofexidine based on FDA-approved indications.

Length of Authorization:
- Up to 14 days

Requires PA:
- Lofexidine 0.18mg tablets

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		
• What diagnosis is being treated?	Record ICD10 code.	
• Is this an FDA approved indication? (Mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults)	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
• 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.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Approve for up to 14 days of total therapy. Note: FDA approved indication is for up to 14 days of therapy AND Notify prescriber concomitant naloxone is recommended if not present in claims history.

P&T/DUR Review: 1/19 (DM)
Implementation: 3/1/19

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Drug Use Evaluation: Antidepressants in Children

Purpose of the Evaluation: Due to limited available evidence on use of tricyclic antidepressants (TCAs) in children and adolescents, the Pharmacy & Therapeutics committee requested an evaluation of antidepressant prescribing patterns in the Oregon Medicaid population with particular focus on evaluation of safe and medically appropriate use of TCAs for children.

Research Questions:

1) How frequently are antidepressants prescribed in children with Food and Drug Administration (FDA)-approved or guideline endorsed indications?
2) Which prescriber types and specialties are associated with antidepressant use in children?
3) Are there antidepressant classes associated with more frequent emergency department visits or hospitalizations?
4) What patient characteristics (relevant diagnoses or prior treatments) are associated with tricyclic antidepressant (TCA) therapy in children?
5) What treatment characteristics (duration of therapy and dose) are associated with TCA therapy in children?

Conclusions:

1. FDA-approved or guideline endorsed indications
    a. Over 13,000 children and adolescents were identified who had claims for an antidepressant therapy over the course of one year. In 74% of patients, prescriptions were filled for a selective serotonin reuptake inhibitor (SSRI), most commonly fluoxetine or sertraline. Paid claims for TCAs were present in 5.6% of the population (n=734), and approximately 245 children less than 12 years of age were prescribed TCAs.
    b. While many antidepressant therapies are not FDA-approved for children, most patients prescribed a SSRI or serotonin norepinephrine reuptake inhibitor (SNRI) had an FDA-approved or compendia-supported indication of depression, anxiety or adjustment reactions. Off-label use of TCAs was more common, and 48% of patients had no FDA-approved indication based on available claims data.
2. Prescriber types and specialties
    a. Pediatric physicians (25%) and providers with a mental health specialty (38%) were the most common prescribers of antidepressant therapy in children and adolescents. Non-specialists including family physicians, family nurse practitioners, and physician assistants accounted for 12%, 7% and 4% of prescribing, respectively.
3. Frequency of emergency department (ED) visits or hospitalizations
    a. There were no large differences in incidence of hospitalization or ED visits based on type of antidepressant. Overall, 17% of patients had an ED visit and 1% of patients had a hospitalization in the 90 days following prescription of an antidepressant.
4. Characteristics associated with TCA therapy
    a. Most patients (65%) with claims for a TCA were classified as treatment-naïve and had had no recent use of other antidepressant therapy in the 4 months prior to their first claim. Almost 33% of patients were prescribed ongoing TCA therapy and few had recent claims for other types of antidepressants.

b. Common psychiatric diagnoses associated with TCA use included anxiety (25%), adjustment disorders (21%), attention deficit hyperactivity disorder (19%), and depression (12%). Common physical health diagnoses included various headache syndromes (36%), and gastrointestinal problems such as abdominal pain, pelvic pain or nausea, and sleep disorders.
c. Approximately 34% of patients were prescribed only short-term use of TCAs with less than 30 days of therapy. Over 45% of patients with claims for a TCA were prescribed therapy for more than 2 months.
d. The average dose for TCAs was less than 50% of the maximum FDA-approved dose in most patients (65-76%). Only a small proportion of patients with claims for TCAs had doses exceeding the FDA maximum dose.

Recommendations:

- Implement a safety edit for initiation of TCA therapy in children younger than the FDA-approved minimum age limit with the goal of preventing off-label use. Automatically approve requests for:
  - Children with prescriptions identified as being written by a mental health specialist, or
  - Children with ongoing TCA therapy, or
  - Children with a recent trial of a SSRI.

Background

Antidepressants are associated with significant safety concerns, particularly in children and adolescents. Many antidepressants are not approved for use in children and most antidepressants have an FDA box warning for increased risk of suicidal thoughts and behavior in pediatric and young adult patients. In particular, TCAs are rarely recommended in pediatric patients less than 12 years of age due to known safety concerns, frequency of adverse events, and limited data on efficacy. Current FDA-approved indications, ages, and maximum doses for TCAs are available in **Appendix 1**.

Recently updated guidance from the National Institute for Health and Care Excellence (NICE) provided recommendations for management of depression in children and young people.[1] Primary first-line therapies for moderate to severe depression include individual or family-based psychotherapy or cognitive behavioral therapy.[1] If pharmacotherapy is needed, fluoxetine is recommended in addition to non-pharmacotherapy for patients 5 to 18 years of age.[1] In patients with depression unresponsive to treatment, recurrent depression or psychotic depression, pharmacotherapy (including fluoxetine, sertraline, citalopram or augmentation with an antipsychotic) may be added to intensive psychological therapy.[1] Pharmacotherapy is not recommended except in combination with concurrent psychological therapy. Recommendations are made against use of paroxetine, venlafaxine, or TCAs for treatment of depression in children.[1]

A 2017 report by the Agency for Healthcare Research and Quality (AHRQ) evaluated evidence for treatment of anxiety in children.[2] Only 19 RCTs (n=2,498) were identified which evaluated pharmacotherapy compared to placebo.[2] SSRIs (fluoxetine, paroxetine, and sertraline) and SNRIs (atomoxetine, duloxetine and venlafaxine) improved primary anxiety symptoms compared to placebo based on moderate to high quality evidence.[2] SSRIs also demonstrated efficacy in improved remission rates, function, and clinical response compared to placebo (moderate to high strength of evidence).[2] TCAs and benzodiazepines lacked conclusive evidence of benefit.[2]

Similarly, guidelines from the American Academy of Neurology and American Headache Society recently updated recommendations for pharmacologic treatment of migraine prevention in pediatric patients and found insufficient evidence to support a reduction in headache frequency with use of amitriptyline monotherapy.[3] When used as monotherapy there was no difference in headache frequency based on one high quality study.[3] However, in patients aged 10-17

years, combined amitriptyline and cognitive behavioral therapy was associated with reduced headache frequency compared to amitriptyline and headache education alone (high strength evidence).[3] Evidence was significantly limited by high placebo response rates (30-61% of children with 50% reduction in headache frequency).[3] Due to the limited evidence available for pharmacologic treatment, recommendations are made to engage in shared decision-making with an adequate discussion of expected risks and benefits of therapy.[3] If benefits may outweigh risks, a short-term (at least 2 month) medication trial may be considered to evaluate utility of prophylactic amitriptyline therapy in combination with cognitive behavioral therapy.[3]

Methods:
Included patients were less than 18 years of age and had a paid FFS pharmacy claim for a drug in the antidepressant PDL class from January 1, 2018 to December 31, 2018. The index event (IE) was defined as the first paid antidepressant claim in the reporting period. Type of antidepressant was categorized according to pharmacologic class (**Appendix 1**) and a subgroup analysis was conducted in patients with an IE for a TCA. Patients were excluded if they had Medicare Part D coverage or less than 75% of covered days in the 120 days before the IE to 120 days after the IE. Baseline characteristics, including patient age, were assessed at the time of the IE.

The following definitions and categories were used for the analysis:

- Duration of therapy was defined using the average days of coverage in the assessment period.
- Prior history of antidepressant use was evaluated in the 120 days prior to the IE and categorized by antidepressant class.
- New start patients were defined as no antidepressant use in the 120 days prior to the IE.
- Prescriber type was identified using the primary provider taxonomy.
- Diagnoses were identified using ICD-10 codes on medical claims in the year prior to the IE (see **Appendix 1** for relevant ICD-10 codes)
- Average daily dose was defined as a percent of the maximum FDA-approved daily dose. If pediatric dosing was not available, maximum adult doses were used (see **Appendix 1**). Daily doses were stratified as greater than the max dose, 51 to 100% of the max dose, and 50% or less of the max dose.
- ED visits and hospitalizations were assessed in the 90 days following the IE. Psychiatric illnesses were defined as visits with a primary ICD-10 diagnosis code beginning with F.

Results:
Most patients with claims for an antidepressant were adolescents older than 13 years of age (68%), white (49%) and female (56%). Most patients prescribed antidepressants received prescriptions for an SSRI (74%), and approximately 53% had no recent history for other antidepressant therapy (**Table 1**). When classified by age, trazodone and mirtazapine were most commonly prescribed for children less than 5 years of age whereas fluoxetine and sertraline were most commonly prescribed in patients 5-17 years of age (**Table 2**). Use of TCAs and SNRIs was infrequent, prescribed for 5.6% (n=734) and 2.9% (n=378) of patients, respectively. The most commonly prescribed TCAs were amitriptyline and nortriptyline.

Over 90% of patients prescribed an SSRI or SNRI had an FDA-approved diagnosis in the year prior to the IE (**Table 3**). However, only 71% of patients prescribed other atypical antidepressants and 52% of patients prescribed TCAs had a documented FDA-approved diagnosis based on medical claims in the year prior to the IE. The most common identified diagnoses were depression, anxiety or panic disorder, and adjustment reactions. The most common prescribers of antidepressants in children and adolescents were pediatric physicians (25%). The top 20 prescriber types are listed in **Table 4**. Practitioners who had a mental health specialty (either nurse practitioners or psychiatric physicians) also accounted for a large majority of prescribing.

Overall, there were no large differences in incidence of hospitalization or ED visits based on type of antidepressant. Approximately 17% of patients had an ED visit and 1% of patients had a hospitalization in the 90 days following prescription of an antidepressant (**Table 5**).

Figure 1. Per member per month (PMPM;unique patient count) from January 2016 to present for children <18 years of age prescribed an antidepressant.

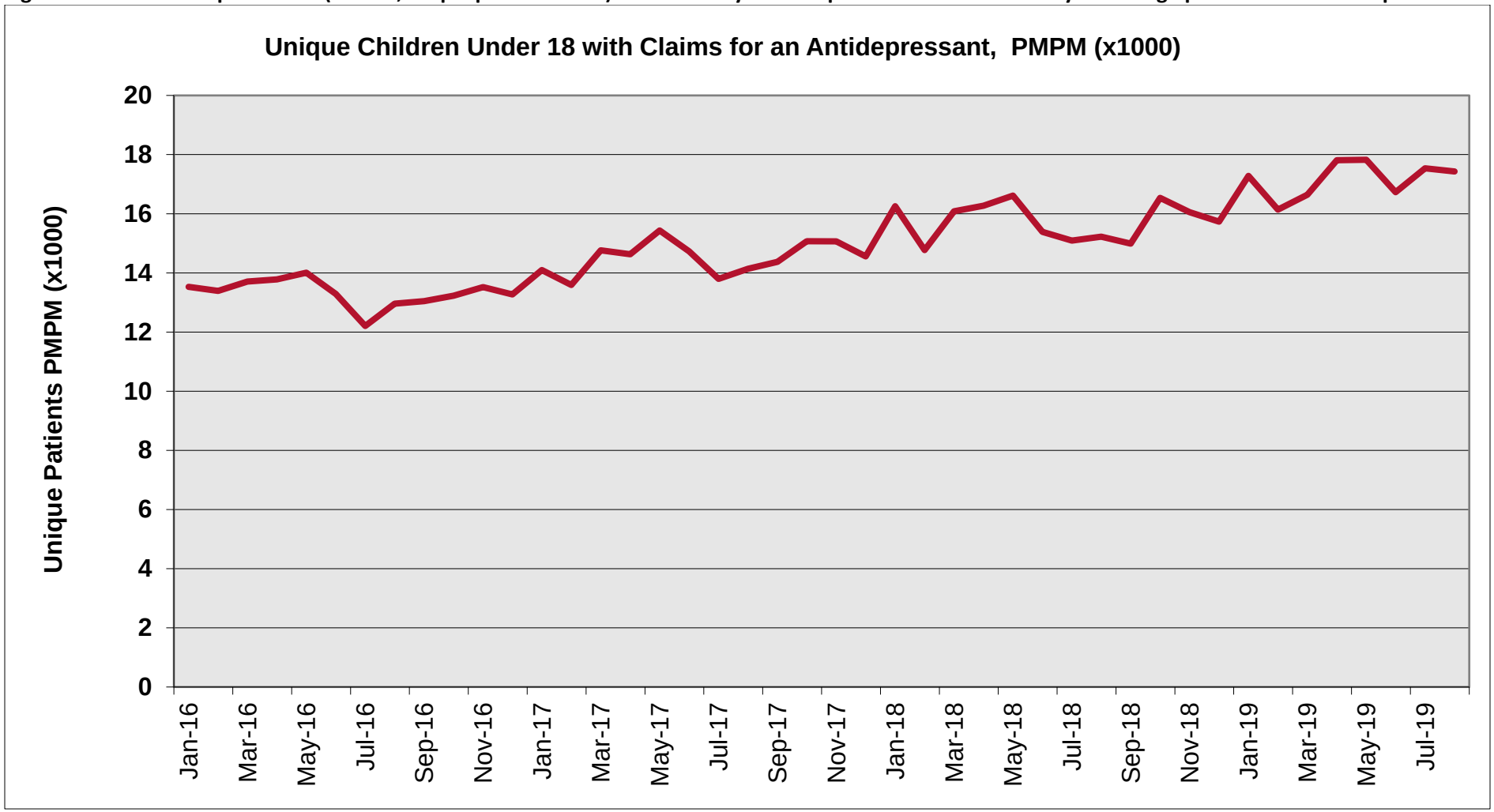

Table 1. Demographics.

	N=	13,058	%
Age			
Average (min - max)		13.3	(0-17)
0-4		58	0%
5-12		4,096	31%
13-17		8,904	68%
Female		7,312	56.0%
Race			
White		6,361	48.7%
Native American		649	5.0%
Other		876	6.7%
Unknown		5,172	39.6%
Antidepressant Class			
SSRI		9,632	73.8%
SNRI		378	2.9%
TCA		734	5.6%
Other		2,314	17.7%
Prior Antidepressant Use			
New start		6,896	52.8%
History of another antidepressant		6,162	47.2%

Table 2. Antidepressant Use by Age

	<5 years		5-12 years		13-18 years	
	58	%	4,096	%	8,904	%
Antidepressant Class						
SSRI	15	25.9%	2,946	71.9%	6,671	74.9%
SNRI	1	1.7%	44	1.1%	333	3.7%
TCA	6	10.3%	239	5.8%	489	5.5%
Other	36	62.1%	867	21.2%	1,411	15.8%

Top 20 Prescribed Antidepressants						
fluoxetine HCl	7	12.1%	1273	31.1%	2540	28.5%
sertraline HCl	6	10.3%	1158	28.3%	2386	26.8%
trazodone HCl	25	43.1%	562	13.7%	779	8.7%
escitalopram oxalate	1	1.7%	230	5.6%	974	10.9%
citalopram hydrobromide		0.0%	229	5.6%	600	6.7%
bupropion HCl		0.0%	106	2.6%	416	4.7%
amitriptyline HCl	**1**	**1.7%**	**134**	**3.3%**	**337**	**3.8%**
mirtazapine	11	19.0%	196	4.8%	200	2.2%
venlafaxine HCl		0.0%	24	0.6%	155	1.7%
duloxetine HCl	1	1.7%	15	0.4%	157	1.8%
paroxetine HCl	1	1.7%	19	0.5%	97	1.1%
fluvoxamine maleate		0.0%	37	0.9%	72	0.8%
nortriptyline HCl	**3**	**5.2%**	**16**	**0.4%**	**85**	**1.0%**
imipramine HCl		**0.0%**	**68**	**1.7%**	**28**	**0.3%**
doxepin HCl		**0.0%**	**11**	**0.3%**	**21**	**0.2%**
desvenlafaxine succinate		0.0%	5	0.1%	19	0.2%
clomipramine HCl		**0.0%**	**5**	**0.1%**	**11**	**0.1%**
vilazodone HCl		0.0%	2	0.0%	12	0.1%
desipramine HCl		**0.0%**	**5**	**0.1%**	**3**	**0.0%**
vortioxetine hydrobromide		0.0%	1	0.0%	4	0.0%

Table 3. Antidepressant Use by FDA-approved Diagnosis. Patients with multiple diagnoses may be counted more than once.

	SSRI		**SNRI**		**TCA**		**Other**	
	9,632	**%**	**378**	**%**	**734**	**%**	**2,314**	**%**
Any FDA-approved indication	8,689	90.2%	345	91.3%	381	51.9%	1,639	70.8%
Depression	4,925	51.1%	242	64.0%	115	15.7%	754	32.6%
Anxiety and Panic disorder	5,838	60.6%	258	68.3%	190	25.9%	898	38.8%
Bipolar Disorder	174	1.8%	16	4.2%	9	1.2%	150	6.5%
Adjustment Reactions	3,613	37.5%	158	41.8%	156	21.3%	859	37.1%
Other FDA-approved indication*	1,207	12.5%	71	18.8%	151	20.6%	285	12.3%
No FDA-approved indication	943	9.8%	33	8.7%	353	48.1%	675	29.2%

* Includes Bulimia nervosa and eating disorders, premenstrual dysphoric disorder/tension syndromes, OCD, smoking cessation (bupropion), diabetic neuropathy, fibromyalgia, chronic pain (SNRIs), and nocturnal enuresis (TCAs).

Table 4. Top 20 Prescriber Types for Antidepressants

Index Prescriber Taxonomy	Patients 13,058	%
PHYSICIAN-PEDIATRICS	3,254	24.9%
NURSE PRACTITIONER - PSYCHIATRIC/MENTAL HEALTH	1,684	12.9%
PHYSICIAN-FAMILY MEDICINE	1,551	11.9%
PHYSICIAN-PSYCHIATRY&NEUROLGY-CHILD&ADOLESCENT PSYCHIATRY	1,523	11.7%
PHYSICIAN-PSYCHIATRY&NEUROLOGY-PSYCHIATRY	1,231	9.4%
NURSE PRACTITIONER - FAMILY	965	7.4%
PHYSICIAN ASSISTANT	608	4.7%
NURSE PRACTITIONER - PEDIATRICS: PEDIATRICS	528	4.0%
PHYSICIAN ASSISTANT - MEDICAL	231	1.8%
PHYSICIAN-PEDIATRICS-DEVELOPMENTAL BEHAVORIAL PEDIATRICS	228	1.7%
STUDENT IN AN ORGANIZED HEALTH CARE EDUCATION/TRAINING PROGRAM	209	1.6%
NURSE PRACTITIONER	151	1.2%
REGISTERED NURSE - PSYCHIATRIC/MENTAL HEALTH	115	0.9%
CLINICAL NURSE SPECIALIST - PSYCHIATRIC/MENTAL HEALTH	99	0.8%
PHYSICIAN-INTERNAL MEDICINE	67	0.5%
PHYSICIAN-PSYCHIATRY&NEUROLOGY-NEUROLOGY	65	0.5%
PHYSICIAN-PEDIATRICS-PEDIATRIC GASTROENTEROLOGY	55	0.4%
PHYSICIAN-PSYCHIATRY&NEUROLOGY-NEUROLOGY WITH SPECIAL QUAL IN CHILD NEUROLO	52	0.4%
PHYSICIAN-PEDIATRICS-ADOLESCENT MEDICINE	38	0.3%
PHYSICIAN-EMERGENCY MEDICINE	36	0.3%

Table 5. Hospitalization and Emergency Department (ED) visits by Antidepressant Class in the 90 days following the IE.

	SSRI		SNRI		TCA		Other		Total	
	9,632	%	378	%	734	%	2,314	%	13,058	%
All ER visits	1,666	17.3%	81	21.4%	129	17.6%	371	16.0%	2,247	17.2%
All hospitalizations	139	1.4%	7	1.9%	17	2.3%	35	1.5%	198	1.5%
ER visit due to psychiatric illness	405	4.2%	23	6.1%	3	0.4%	80	3.5%	511	3.9%
Hospitalization due to psychiatric illness	108	1.1%	6	1.6%	7	1.0%	26	1.1%	147	1.1%

Subgroup analysis in patients with a TCA index event

Most common relevant psychiatric and physical diagnoses in patients with TCA use are listed in **Table 6**. Because medications are not associated with diagnoses codes, it is difficult to determine the exact diagnosis intended for the medication. TCAs have a wide variety of adverse effects and they are commonly used off-label despite insufficient or inconclusive evidence of benefit in pediatric populations. Documented off-label indications include various types of pain (e.g., headache, cancer pain, fibromyalgia, neuropathy), gastrointestinal syndromes (e.g., irritable bowel syndrome, nocturnal enuresis, urinary incontinence, neurogenic bladder), and psychiatric conditions (insomnia, ADHD, premenstrual dysphoric disorder, smoking cessation assistance, binge eating disorder).[4] In children prescribed TCAs, the most common psychiatric diagnoses included anxiety (25%), adjustment disorders (21%), ADHD (19%), and depression (12%). Common non-psychiatric diagnoses included various headache syndromes (36%), and gastrointestinal problems such as abdominal pain, pelvic pain or nausea, and sleep disorders.

Most patients with claims for a TCA were classified as treatment-naïve and had had no recent use of other antidepressant therapy in the 4 months prior to their first claim (65%; **Table 7**). Thirty-three percent of patients were prescribed ongoing TCA therapy, and only a small percent had claims indicating they may be switching from a different antidepressant class. Approximately 34% of patients were prescribed only short-term use of TCAs with less than 30 days of therapy. Over 45% of patients with claims for a TCA were prescribed therapy for more than 2 months. On average, the TCA dose was less than 50% of the maximum FDA approved dose in most patients (65-76%). Only a small proportion of patients had TCA doses prescribed above the recommended maximum dose (2-6%).

Table 6. Common Diagnoses in Patients Prescribed TCAs.

Diagnosis grouped by category using the first 3 characters of the ICD-10 code. ICD-10 codes beginning with Z (factors influencing health status) were excluded.

		TCA Patients	
Diagnosis in year prior to IE		**734**	**%**
Psychiatric Diagnoses			
F41	Other anxiety disorders	184	25.1%
F43	Reaction to severe stress, and adjustment disorders	156	21.3%
F90	Attention-deficit hyperactivity disorders	142	19.3%
F32	Major depressive disorder, single episode	91	12.4%
F91	Conduct disorders	54	7.4%
F07	Personality & behavioral disorders due to known physiological condition	47	6.4%
F33	Major depressive disorder, recurrent	46	6.3%
F34	Persistent mood [affective] disorders	36	4.9%
F51	Sleep disorders not due to a substance or known physiological condition	36	4.9%
Relevant Physical Diagnoses			
G43	Migraine	266	36.2%
R51	Headache	262	35.7%
R10	Abdominal and pelvic pain	206	28.1%
R11	Nausea and vomiting	170	23.2%
G44	Other headache syndromes	124	16.9%
G47	Sleep disorders	117	15.9%
M54	Dorsalgia	112	15.3%

K59	Other functional intestinal disorders	99	13.5%
N39	Other disorders of urinary system	99	13.5%
R53	Malaise and fatigue	83	11.3%
R42	Dizziness and giddiness	64	8.7%
E66	Overweight and obesity	63	8.6%
R19	Other symptoms and signs involving the digestive system and abdomen	63	8.6%
R07	Pain in throat and chest	62	8.4%
G89	Pain, not elsewhere classified	60	8.2%
R30	Pain associated with micturition	53	7.2%
K21	Gastro-esophageal reflux disease	51	6.9%
R41	Other symptoms and signs with cognitive functions and awareness	46	6.3%
R45	Symptoms and signs involving emotional state	44	6.0%
N92	Excessive, frequent and irregular menstruation	43	5.9%

Table 7. Prior Antidepressant Use in Patients with TCAs.

Utilization was assessed in the 120 days prior to the IE. Patients with claims for multiple types of antidepressants may be counted more than once.

	Patients with TCA IE	
	734	**%**
Treatment-naïve	477	65.0%
Prior Antidepressant Use		
SSRI	42	5.7%
SNRI	3	0.4%
TCA	239	32.6%
Other	20	2.7%

Table 8. Duration of TCA Use.

Assessed by the average days of coverage in 120 days following IE.

	Patients with TCA IE	
Days of Coverage	**734**	**%**
<=7 days	2	0.3%
8-30 days	250	34.1%
31-60 days	149	20.3%
61-120 days	333	45.4%

Table 9. TCA Dose at IE and for Patients Prescribed Continuous Therapy.

Maximum dose defined according to FDA-approved pediatric doses (when available) or adult maximum doses in **Appendix 1**. In patients with ongoing therapy for more than 60 days, average dose calculated based on most recent claim in the 120 days following IE.

	IE Dose		Patients with >60 days of coverage	
Average Daily Dose	**734**	**%**	**333**	**%**
<=50% of FDA max dose	558	76.0%	218	65.5%
51-100% of FDA max dose	157	21.4%	94	28.2%
> 100% of FDA max dose	19	2.6%	21	6.3%

Limitations:

Data presented in this report is based on Medicaid claims history and has several inherent limitations.

- Diagnostic accuracy: Diagnoses based on claims history may be inaccurate or incomplete. Because diagnoses are not associated with prescriptions, it is difficult to determine the intended indication for the drug, particularly when therapy is used off-label.
- Provider specialty: Information on provider specialty may be inaccurate, out-of-date, or incomplete for some providers. Prescribers with multiple specialties or designations may not be identified.
- Days of coverage: Estimates of covered days attempts to approximate the frequency which a patient takes a prescription, but accuracy of this method has not been validated, covered days may not accurately correlate to actual medication adherence, and patients may not always be categorized appropriately.
- Definitions for treatment-naïve patients: Prior use of antidepressants was only evaluated in the 120 days prior to the IE. Patients may have a remote history of antidepressant use beyond this date which could influence choice in current therapy.

References:

1. National Institute for Health and Care Excellence. Depression in children and young people: identification and management. Clinical Guideline. September 2017. Available at: www.NICE.org.uk. Accessed: July 30, 2019.
2. Wang Z WS, Sim L, et al. Anxiety in children. Comparative Effectiveness Review No. 192. AHRQ Publication No. 17-EHC023-EF. Rockville, MD. Agency for Healthcare Research and Quality. August 2017.
3. Oskoui M, Pringsheim T, Billinghurst L, et al. Practice guideline update summary: Pharmacologic treatment for pediatric migraine prevention. *Neurology.* 2019;93(11):500.
4. Micromedex Healthcare Series [internet database]. Greenwood Village, CO: Truven Health Analytics, Inc. Updated periodically. Accessed August 13, 2019.

Appendix 1: Coding Information

Table A1. Antidepressant Classes and FDA approved Ages[4]

Class	HSN	Generic Name	FDA Approval in Children
Other	001638	isocarboxazid	≥16 years
Other	001639	phenelzine sulfate	NA
Other	033510	selegiline	NA
Other	001640	tranylcypromine sulfate	NA
Other	036156	bupropion HBr	NA
Other	001653	bupropion HCl	NA
Other	011505	mirtazapine	NA
Other	009612	nefazodone HCl	NA
Other	001652	trazodone HCl	NA
Other	037597	vilazodone HCl	NA
Other	040637	vortioxetine hydrobromide	NA
SNRI	040202	desvenlafaxine	NA
SNRI	040692	desvenlafaxine fumarate	NA
SNRI	035420	desvenlafaxine succinate	NA
SNRI	026521	duloxetine HCl	≥7 years (anxiety)
SNRI	040632	levomilnacipran HCl	NA
SNRI	008847	venlafaxine HCl	NA
SSRI	010321	citalopram hydrobromide	NA
SSRI	024022	escitalopram oxalate	≥12 years (MDD)
SSRI	001655	fluoxetine HCl	≥7 years (MDD, OCD, bipolar)
SSRI	006338	fluvoxamine maleate	≥8 years (OCD)
SSRI	025800	olanzapine/fluoxetine HCl	≥10 years (bipolar)
SSRI	007344	paroxetine HCl	NA
SSRI	025796	paroxetine mesylate	NA
SSRI	006324	sertraline HCl	≥6 years (OCD)
TCA	001643	amitriptyline HCl	≥12 years (MDD)
TCA	001648	amoxapine	NA
TCA	004744	clomipramine HCl	≥10 years (OCD)
TCA	001645	desipramine HCl	NA
TCA	001650	doxepin HCl	≥12 years (anxiety, MDD)
TCA	001641	imipramine HCl	≥6 years (nocturnal enuresis)
TCA	001642	imipramine pamoate	NA
TCA	001651	maprotiline HCl	NA
TCA	001644	nortriptyline HCl	≥12 years (MDD)
TCA	001646	protriptyline HCl	≥12 years (MDD)
TCA	001649	trimipramine maleate	≥12 years (MDD)

Abbreviations: MDD = major depressive disorder; NA = not applicable; OCD = obsessive compulsive disorder; SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant

Table A2. TCA Max Dose Definitions[4]

Class	HSN	Generic	FDA Max Daily Dose	Source of max dose (pediatric if available or adult)
TCA	001643	amitriptyline HCl	50 mg	Pediatric
TCA	001648	amoxapine	400 mg	Adult
TCA	004744	clomipramine HCl	200 mg	Pediatric
TCA	001645	desipramine HCl	300 mg	Adult
TCA	001650	doxepin HCl	150 mg	Pediatric
TCA	001641	imipramine HCl	75 mg	Pediatric
TCA	001642	imipramine pamoate	200 mg	Adult
TCA	001651	maprotiline HCl	225 mg	Adult
TCA	001644	nortriptyline HCl	50 mg	Pediatric
TCA	001646	protriptyline HCl	60 mg	Adult
TCA	001649	trimipramine maleate	100 mg	Pediatric

Table A3. Antidepressant Dosing Calculations for Unique Formulations

GSN	Route	Form	Strength	Generic	Mg per Unit
046092	PO	ORAL CONC	10 mg/mL	doxepin HCl	10
046063	PO	SOLUTION	10 mg/5 mL	nortriptyline HCl	2
078426	PO	SOLUTION	20 mg/10 mL	nortriptyline HCl	2

Table A4. ICD-10 diagnosis codes

ICD10	ICD-10 Description	Category
F31xx	Bipolar disorder	Bipolar Disorder
F32xx (excluding F32.81)	Major depressive disorder, single episode	Depression
F33xx	Major depressive disorder, recurrent	Depression
F41xxx	Other anxiety disorders	Panic or anxiety disorder
F40xxx	Phobic anxiety disorders	Panic or anxiety disorder
F43xxx	Reaction to severe stress, and adjustment disorders	Adjustment disorders
F42XX	Obsessive-compulsive disorders	Other indications
N94.3	Premenstrual tension syndrome	Other indications
F32.81	Premenstrual dysphoric disorder	Other indications
F50xx	Eating disorders	Other indications
F17xx	Nicotine dependence	Other indications
E11.40	Diabetes with neuropathy	Other indications
M79.7	Fibromyalgia	Other indications
G89.2x	Chronic pain, not elsewhere classified	Other indications
N39.44	Nocturnal enuresis	Other indications

Tricyclic Antidepressants

Goal(s):

- Ensure safe and appropriate use of tricyclic antidepressants in children less than 12 years of age
- Discourage off-label use not supported by compendia

Length of Authorization:

Up to 12 months

Requires PA:

- Tricyclic antidepressants in children younger than the FDA-approved minimum age (new starts)
- Auto-PA approvals for:
  - Patients with a claim for an SSRI or TCA in the last 6 months
  - Prescriptions identified as being written by a mental health provider

Covered Alternatives:

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

Table 1. FDA-Approved Indications of Tricyclic Antidepressants

Drug	FDA-Approved Indications	Maximum Dose	Minimum FDA-Approved Age
amitriptyline HCl	Depression	50 mg	12
amoxapine	Depression	400 mg	18
clomipramine HCl	Obsessive-compulsive disorder	200 mg	10
desipramine HCl	Depression	300 mg	18
doxepin HCl	Depression Anxiety	150 mg	12
imipramine HCl	Depression Nocturnal enuresis	75 mg	6
imipramine pamoate	Depression	200 mg	18
maprotiline HCl	Depression Bipolar depression Dysthymia Mixed anxiety and depressive disorder	225 mg	18
nortriptyline HCl	Depression	50 mg	12

protriptyline HCl	Depression	60 mg	12
trimipramine maleate	Depression	100 mg	12

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Does the dose exceed the maximum FDA-approved dose (**Table 1**)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #4
4. Is the request for an FDA-approved indication and age (**Table 1**)?	**Yes:** Approve for up to 6 months	**No:** Go to #5
5. Is the request for prophylactic treatment of headache or migraine and is the therapy prescribed in combination with cognitive behavioral therapy?	**Yes**: Approve for up to 6 months	**No:** Go to #6
6. Is the drug prescribed by or in consultation with an appropriate specialist for the condition (e.g., mental health specialist, neurologist, etc.)?	**Yes**: Approve for up to 6 months	**No:** Pass to RPh. Deny; medical appropriateness.

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Prior Authorization Criteria Update: Dupilumab

Purpose of Update:

Dupilumab was recently reviewed by the Pharmacy and Therapeutics (P and T) Committee at the July 2019 meeting. To support administration of PA criteria, dupilumab was removed from atopic dermatitis (AD) and topical antipsoriatic prior authorization (PA) criteria and a new PA document to support dupilumab utilization in moderate-to-severe asthma and moderate-to-severe AD was approved. In June 2019, dupilumab received Food and Drug Administration (FDA) approval as add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP).[1] Chronic sinusitis is funded condition on line 463 of the Oregon Health Evidence Review Commission's prioritized list of health conditions.[2] This update evaluates evidence for dupilumab use in CRSwNP.

Background:

Chronic rhinosinusitis with nasal polyposis (CRSwNP) is an inflammatory disease of the nasal and paranasal mucosa, which causes symptoms of nasal obstruction, decreased sense of smell, facial pain, headache, and rhinorrhea. Typically observed in the context of eosinophilic inflammation of the upper airways, nasal polyps originate in the sinuses and obstruct the sinus and nasal passages.[3] Therapy for CRSwNP includes nasal saline irrigations and intranasal corticosteroid sprays for maintenance therapy, and systemic corticosteroids with antibiotics for acute exacerbations.[4] If patients do not experience symptom relief, endoscopic sinus surgery may be considered in order to alleviate obstruction, remove inflammatory tissue, and facilitate delivery of topical therapies.[4] Research has been directed toward a better understanding of the inflammatory pathways in CRSwNP so that more targeted biologic therapies can be developed. Omalizumab, mepolizumab, and reslizumab are currently being studied as treatment options in adults with CRSwNP.

The FDA approved dupilumab as add-on maintenance treatment in adults patients with inadequately controlled CRSwNP based on data from 1 randomized controlled trial (RCT).[1] This trial was a randomized, double-blind, placebo-controlled, parallel-group study conducted at 13 sites in the United States and Europe in 60 adults aged 18 to 65 years with CRSwNP refractory to intranasal corticosteroids.[3] Patients were randomized to receive subcutaneous dupilumab (a 600 mg loading dose followed by 300 mg weekly (n = 30); or placebo (n = 30) plus mometasone furoate nasal spray twice daily for 16 weeks.[3] The primary endpoint was mean change in bilateral endoscopic nasal polyp score from baseline to week 16.[3] This score is graded based on polyp size (recorded as the sum of the right and left nostril scores with a range of 0-8; higher scores indicate worse status).[3] Of note, a minimal clinically important difference (MCID) for nasal polyp score has not yet been established.[3] Subjects enrolled in this trial were required to have a bilateral endoscopic nasal polyp score of at least 5 (maximum score of 8), with a score of at least 2 for each nostril, and have at least 2 of the following symptoms prior to screening: nasal obstruction or discharge, facial pain or pressure, and reduction or lost sense of smell.[3]

The least squares mean (LSM) change in bilateral endoscopic nasal polyp score between baseline and week 16 was −0.3 in the placebo group and −1.9 in the dupilumab group (LSM difference −1.6; 95% CI, −2.4 to −0.7; P<0.001).[3] Adverse events were reported by 25 of 30 patients in the placebo group and 30 of 30 in the dupilumab group.[3] Mild-to-moderate nasopharyngitis (33% in the placebo group vs. 47% in the dupilumab group), injection site reactions (7% vs. 40%,

respectively), and headache (17% vs. 20%, respectively) were the most frequently reported adverse events.[3] This was small trial of limited duration; therefore, there is insufficient evidence to assess the effect of long-term treatment of CRSwNP with dupilumab. The study was funded by Sanofi and Regeneron Pharmaceuticals. The manufacturers, in collaboration with the academic clinical investigators, provided input on the design and conduct of the study; oversaw the collection, management, and statistical analysis of data; and contributed to the interpretation of the data and the preparation, review, and submission of the manuscript.[3]

Data from 2 additional trials (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52) were published in September 2019. The 2 trials evaluated the safety and efficacy of dupilumab in treating adults with severe CRSwNP previously treated with systemic corticosteroids and/or surgery.[5] The trial design was similar for both studies: international, multicenter, randomized, double-blind, placebo-controlled, parallel-group assessment of dupilumab added to standard of care in adults with severe CRSwNP.[5] SINUS-24 was conducted in 67 centers in 13 countries (Bulgaria, Czechoslovakia, France, Germany, Hungary, Italy, the Netherlands, Poland, Romania, Ukraine, Russia, United Kingdom, and United States). Patients (n=276) in SINUS-24 were randomized 1:1 to receive either to subcutaneous dupilumab 300 mg or placebo every 2 weeks for 24 weeks. SINUS-52 was conducted in 117 centers in 14 countries (Argentina, Australia, Belgium, Canada, Chile, Israel, Mexico, Portugal, Russia, Spain, Sweden, Turkey, Japan, and United States).[5] Patients in SINUS-52 (N=448) were randomized 1:1:1 to dupilumab 300 mg every 2 weeks for 52 weeks, dupilumab 300 mg every 2 weeks for 24 weeks and then 300 mg every 4 weeks for the remaining 28 weeks, or placebo every 2 weeks for 52 weeks.[5] Inclusion criteria were similar to the first RCT that evaluated the use of dupilumab in treating patients with CRSwNP.

The co-primary endpoints in both studies were change from baseline in both endoscopic nasal polyp score and nasal congestion severity (based on monthly average of daily score recorded by patients) at week 24.[5] Change from baseline in nasal congestion severity was assessed by a visual analog scale (score 0-3).[5] In SINUS-24, the LSM change in bilateral endoscopic nasal polyp score between baseline and week 24 was 0.17 in the placebo group and −1.9 in the dupilumab group (LSM difference –2.06; 95% CI, –2.43 to –1.69; p<0.0001).[5] Similar results were observed in SINUS-52, as the LSM change in bilateral endoscopic nasal polyp score between baseline and week 24 was 0.1 in the placebo group and −1.7 in the dupilumab group (LSM difference–1.80; 95% CI, –2.10 to –1.51; p<0.0001).[5] The difference in nasal congestion or obstruction score favored dupilumab over placebo at week 24 in SINUS-24 (LSM difference −0.89; 95% CI, –1.07 to –0.71; p<0.0001) and SINUS-52 (LSM difference −0.87; 95% CI, –1.03 to –0.71; p<0·0001).[5]

The most common adverse events (nasopharyngitis, worsening of nasal polyps and asthma, headache, epistaxis, and injection-site erythema) were more frequent with placebo than dupilumab over the 24 week treatment period.[5] In SINUS-52, treatment-emergent adverse events of worsening of nasal polyps and asthma and of sinusitis, arthralgia, and accidental overdose occurred more frequently in patients who switched from dupilumab every 2 weeks to every 4 weeks than in those who remained on dupilumab every 2 weeks for the full 52 weeks.[5] Dupilumab as monotherapy for treating CRSwNP has not been evaluated. Both trials were funded by Sanofi and Regeneron Pharmaceuticals.

Recommendation:

- Revise dupilumab PA criteria to include CRSwNP as an FDA-approved indication for dupilumab as add on therapy to standard of care for CRSwNP (**Appendix 1**).

References:

1. Dupixent® (dupilumab) Prescribing Information. Bridgewater,NJ; Sanofi-Aventis. June 2019.
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3. Bachert C, Mannent L, Naclerio RM, et al. Effect of Subcutaneous Dupilumab on Nasal Polyp Burden in Patients With Chronic Sinusitis and Nasal Polyposis: A Randomized Clinical TrialSubcutaneous Treatment for Chronic Sinusitis With Nasal PolyposisSubcutaneous Treatment for Chronic Sinusitis With Nasal Polyposis. *Jama.* 2016;315(5):469-479.
4. Kartush AG, Schumacher JK, Shah R, Patadia MO. Biologic Agents for the Treatment of Chronic Rhinosinusitis With Nasal Polyps. *Am J Rhinol Allergy.* 2019;33(2):203-211.
5. Bachert C, Han JK, Desrosiers M, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. *Lancet (London, England).* 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, otolaryngologist, or allergist who specializes in management of severe asthma?	**Yes:** Go to # 7	**No:** Pass to RPh. Deny; medical appropriateness
7. What is the age of the patient? • Dupilumab injection is FDA approved for patients 12 years of age and older	**Age 11 years or younger**: Pass to RPh. Deny; medical appropriateness.	**Ages 12 years and older:** Go to #8
8. Is the diagnosis Moderate/Severe Atopic Dermatitis (AD)?	**Yes:** Go to #9	**No:** Go to #10

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

Approval Criteria		
13. Has the patient been adherent to current asthma therapy in the past 12 months?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness.
14. Does the patient have chronic rhinosinusitis with nasal polyposis?	**Yes:** Go to # 15	**No:** Pass to RPh. Deny; medical appropriateness.
15. Has the patient failed medical therapy with inhaled corticosteroids (2 or more courses of adequate doses)?	**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.
3. Is the request to renew dupilumab for moderate to severe asthma?	**Yes:** Go to # 4	**No:** Go to # 6

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

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

Implementation: *TBD: 8/19/19*

Drug Use Research & Management Program
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New Drug Evaluation: Aemcolo™ (rifamycin) delayed release tablet, oral

Date of Review: November 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/NNT	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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15. Aemcolo (rifamycin) Prescribing Information. San Diego, CA; Aries Pharmaceuticals, Inc. 11/2018.
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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

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.

1. Riddle MS, DuPont HL, Connor BA. ACG Clinical Guideline: Diagnosis, Treatment, and Prevention of Acute Diarrheal Infections in Adults. Am J Gastroenterol. 2016;111(5):602-622

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: Arikayce™ (amikacin liposome) suspension for oral inhalation

Date of Review: November 2019
Generic Name: amikacin liposome inhalation suspension

End Date of Literature Search: September 2019
Brand Name (Manufacturer): Arikayce® (Insmed Incorporated)
Dossier Received: yes

Research Questions:

1. What is the efficacy of amikacin liposome inhalation suspension compared to placebo or currently available therapy for treatment-refractory mycobacterium avian complex (MAC) lung disease?
2. Is amikacin liposome inhalation suspension safer than alternative therapeutic agents used in treatment-refractory MAC lung disease?
3. Are there any subgroups (based on age, ethnicity, comorbidities, disease duration or severity) that would particularly benefit or be harmed from treatment with amikacin liposome inhalation suspension?

Conclusions:

- There is low quality evidence based on one phase 2 randomized controlled trial (RCT) that amikacin liposome inhalation suspension 590 mg resulted in a greater proportion of patients with one negative sputum culture by month 6 compared to placebo in patients with treatment-refractory Mycobacterium Avian Complex (MAC) lung disease (31.8% vs. 8.9%, respectively, p=0.0057; Number Needed to Treat [NNT]=5).[1,2]
- There is low quality of evidence based on one phase 3 open label trial that amikacin liposome inhalation suspension 590 mg plus an optimized background antibacterial regimen (OBR) demonstrated a greater proportion of patients with sputum culture conversions at month 6 compared to OBR alone in patients with treatment-refractory MAC lung disease (29.0% vs. 8.9%, respectively, adjusted odds ratio 4.22; 95% CI, 2.08 to 8.57; p<0.0001; NNT=5).[2,3] Culture conversion was defined as 3 consecutive monthly MAC-negative sputum cultures by month 6 of the study. [2,3]
- There is insufficient evidence that use of amikacin liposome inhalation suspension in patients with treatment-refractory MAC lung disease is associated with any clinically significant change in functional status. Functional improvement was evaluated with the 6-minute walk test (6MWT). [1-3] The phase 2 study reported a statistically significant difference in 6MWT distance from baseline to day 84 that favored the amikacin group compared to placebo (20.6 m increase vs. 25 m decrease, respectively, p=0.0102), but no statistically significant difference was observed for the same endpoint in the phase 3 study. [1-3]
- There is low quality evidence of increased discontinuations due to adverse events and serious adverse events in patients treated with amikacin liposome inhalation suspension compared to patients on a background regimen alone for treatment-refractory MAC lung disease.[1-4] The FDA issued a Black Boxed Warning regarding amikacin liposome inhalation suspension for increased risk of respiratory adverse reactions including hypersensitivity pneumonitis, hemoptysis, bronchospasm, and exacerbation of underlying pulmonary disease that have led to hospitalizations.[4] The safety of amikacin liposome inhalation suspension has not been evaluated in pregnancy, breastfeeding women, pediatric patients, or patients with hepatic or renal impairment.[2,4]

Author: David Engen, PharmD

Recommendations:

- Designate amikacin liposome inhalation suspension as non-preferred on the preferred drug list (PDL).
- Implement clinical prior authorization criteria for amikacin liposome inhalation suspension to ensure appropriate utilization (**Appendix 2**).

Background:

Nontuberculosis mycobacteria (NTM) encompass a broad spectrum of mycobacterial pathogens some of which are a frequent cause of skin and soft tissue infection, lung disease, and disseminated disease.[5] NTM lung disease is a progressive and debilitating condition that is a major public health concern with annual United States (U.S.) health care cost of roughly $1.7 billion.[6] Risks for development of NTM pulmonary disease include host factors such as the presence of structural lung defects (e.g. COPD or bronchiectasis), certain genetic disorders (e.g. cystic fibrosis [CF]), or host-susceptibility (e.g. hypersensitivity pneumonitis or weakened immune responses due to HIV). [5,7] Patients treated with particular pharmacological agents may also be at increased risk of NTM lung disease such as those on chronic gastric acid suppression and individuals treated with immunosuppressive agents such as TNF-alpha inhibitors and corticosteroids. [5,7,8] NTM lung disease may also occur in individuals without any known predisposing condition.[5,9] The most frequent group of NTM organisms responsible for pulmonary infection in the U.S. is free-living Mycobacterium Avian Complex (MAC). [7,8] Lung infections caused by MAC (*M. avium*, *Mycobacterium intracellulare,* and *M. chimaera*) can result in irreversible bronchial damage and increased mortality. [9]

MAC is commonly found throughout the environment in soil, groundwater, and surface water but is usually not of great pathologic concern.[10] These mycobacteria are aerobic, non-motile microorganisms with a dense lipid cell wall.[5] The waxy protective cell envelope enables MAC to be resistant to most disinfectants, high temperatures, and antibiotics.[5] With its ability to withstand environmental insult, MAC can easily colonize treated indoor water systems such as swimming pools and hot tubs.[11,12] The glycopeptidolipids produced by NTM form a biofilm to enhance survival even in showerheads and household plumbing.[5] Due to its hydrophobic nature, MAC can aerosolize from water and spread via inhalation from contaminated sources, but there is little evidence to demonstrate person-to-person transmission of MAC.[12] Although MAC is generally not a concern for disease in healthy individuals, pathogenic capability may vary based on host susceptibility, pathogen virulence, and environmental risk factors.[5,9] MAC can cause progressive lung disease and subsequent respiratory failure even in individuals with no history of smoking or underlying lung disease as seen in a type of nodular bronchiectasis known as Lady Windermere Syndrome.[13] MAC disease prevalence has significantly increased in recent years and is most common in parts of Northern Europe, Japan, and the United States, particularly in the West and Southwest regions.[14] In a large study at 56 sites worldwide, MAC was isolated in 47% of the NTM-related pulmonary disease cases.[14] Early Centers for Disease Control and Prevention (CDC) data collected in the U.S. found higher rates of NTM lung disease in women, African Americans, and Hispanics.[9] In 2018, there were 32 unique cases of pulmonary mycobacterial infection identified from claims data in the Oregon Medicaid Fee-for-Service (FFS) population.

The American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) guidelines define NTM lung disease as the presence of pulmonary symptoms, nodular or cavitary opacities on chest radiograph, or multifocal bronchiectasis with nodules on chest X-ray/CT scan, plus positive cultures from either two sputum samples, one bronchoalveolar wash or lavage, or one lung biopsy.[11] MAC symptoms are non-specific and may present differently if the patient has pre-existing lung disease such as COPD or bronchiectasis.[13] Asymptomatic cases may be discovered by a fortunate chest radiograph screening, however, even symptomatic cases may remain undetected for months to years before diagnosis.[9,11] Non-specific warning signs such as chronic cough, dyspnea, and malaise are common, but fever, hemoptysis and weight loss may also occur, especially in fibrocavitary disease.[9,11] Treatment for MAC lung disease are generally dependent upon radiologic criteria and cultures to determine the appropriate regimen.[9,11] Patients with nodular bronchiectatic disease tend to progress much more slowly than fibrocavitary disease and may require long follow-up periods to observe clinical or radiographic changes.[9,11] Therefore, frequent clinical monitoring, routine sputum cultures, and radiographic imaging may be preferred until risks of multi-drug therapy are weighed against benefits of treatment.[9,11] However, patients

with fibrocavitary disease (cavities, fibrosis, and pleural involvement) generally require more aggressive treatments at the time of initial diagnosis due to the rapid progression and destructive nature of this type of disease.[9,11]

ATS-IDSA guidelines suggest that the medical treatment regimen chosen for MAC lung disease be driven by the clinical presentation and individual goals of therapy for each patient (see **Table 1**).[11] Treatment typically consists of a combination of a rifamycin, ethambutol, and a macrolide until sputum cultures become negative and then ongoing treatment for 12 months.[11] Previous studies had reported 20-90% treatment success rates for MAC lung disease with the 3-drug regimen, but estimates were closer to 40% when discontinuations, relapses, surgical requirements and deaths were included in the calculation.[9] For nodular/bronchiectatic disease, a three times per week regimen is preferred for due to better tolerability.[11] For cavitary disease, however, a daily 3-drug regimen is preferred. In the cases of advanced MAC disease or those previously treated, the addition of an intravenous aminoglycoside active against MAC is preferred.[11]

Table 1. Therapy for Mycobacterium Avium Complex Lung Disease: Recommendations According to Disease Status and/or Severity (modified) [11]

Condition	Drug Class	Agent/Dose	Evidence Quality [b]
Initial Therapy for Nodular/Bronchiectatic Disease [a]	Macrolide	Clarithromycin 1000 mg TIW or azithromycin 500-600 mg TIW	B, II
	Ethambutol	25 mg/kg TIW	
	Rifamycin	Rifampin 600 mg TIW	
	IV aminoglycoside	None	
Initial Therapy for Cavitary Disease	Macrolide	Clarithromycin [c] 500-1000 mg daily or azithromycin 250-300 mg daily	A, II
	Ethambutol	15 mg/kg daily	
	Rifamycin	Rifampin [c] 450-600 mg daily	
	IV aminoglycoside	Streptomycin or amikacin [d] or none	
Advanced (Severe) or Previously Treated Disease	Macrolide	Clarithromycin [c] 500-1000 mg daily or azithromycin 250-300 mg daily	B, II
	Ethambutol	15 mg/kg daily	
	Rifamycin	Rifabutin [c] 150-300 mg daily or rifampin 450-600 mg daily	
	IV aminoglycoside	Streptomycin or amikacin [d]	
Category A = Good evidence to support a recommendation for use Category B = Moderate evidence to support recommendation for use Grade II = Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center, from multiple time-series studies or from dramatic results in uncontrolled experiments			

Abbreviations: IV = intravenous; TIW = three times weekly

Note: *a* = Not recommended for severe or previously treated disease; *b* = Rating for entire multidrug regimen; *c* = Lower dose for weight < 50kg; *d* = variable dosing; see original document for details

Clinical outcome definitions for NTM treatment have been developed by the Nontuberculosis Mycobacteria Network European Trials group (NMT-MET) to improve consistency in the interpretation of therapy efficacy (see **Table 2**).[15] Culture conversion may require 3 to 6 months, but inability to convert sputum to

culture negative by 6 months is generally recognized as treatment failure or refractory disease.[12,15] Patients who do not respond to first-line therapy have limited treatment options which may require expert consultation and the possibility of surgical resection.[12]

Table 2. Treatment Outcome Definitions for Nontuberculous Mycobacterial Pulmonary Disease [15]

Outcome	Definition
Culture conversion	≥ 3 consecutive negative mycobacterial cultures from respiratory samples collected ≥ 4 weeks apart during treatment
Microbiologic cure	Multiple consecutive negative and no positive cultures with the causative species from respiratory samples after culture conversion through the end of treatment
Clinical cure	In the absence of evidence of culture conversion or microbiologic cure, patient-reported and/or objective improvement in symptoms on treatment that is sustained through end of treatment
Cure	Treatment completion with both microbiologic and clinical cure
Treatment failure	Re-emergence of ≥ 2 positive cultures or persistence of positive cultures with causative species from respiratory samples after ≥ 12 months of treatment while still on treatment
Recurrence	Re-emergence of ≥ 2 positive cultures with causative species from respiratory samples after ending treatment; may be relapse or reinfection
Relapse	Emergence of ≥ 2 positive cultures with same causative strain after treatment
Reinfection	Emergence of ≥ 2 positive cultures with a different causative strain after treatment

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:

In September 2018, the U.S. Food and Drug Administration (FDA) approved amikacin liposome inhalation suspension (Arikayce®) for the treatment of patients with refractory MAC lung disease.[2] Amikacin liposome inhalation suspension (ALIS) is an antibacterial aminoglycoside that disrupts and inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit.[2,4] The positively charged molecules enter the bacterial cell and interact with negatively charged particles on the cell surface to disrupt cell wall integrity which ultimately leads to bacterial cell death.[2,4] ALIS is indicated for adults who have limited or no alternative treatment options for MAC lung disease as part of a combination antibacterial drug regimen in patients who do not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy.[2,4] ALIS was approved under the Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD) as an antibacterial agent intended to treat a serious infection in a very limited population with unmet needs.[2,4] The evidence did not support a favorable benefit-risk profile for use in a broader population of patients with non-refractory MAC lung disease.[2,4] The efficacy and safety of ALIS for this indication was evaluated with data from one phase 2 trial and one phase 3 trial which are described below and summarized in **Table 5.**

Study 112 was a 12-week, phase 2 double blind RCT (N=89) to evaluate the safety and tolerability of ALIS 590 mg (n=44) compared to placebo (n=45) plus guideline-based background therapy (GBT) (Table 1) in patients with treatment-refractory NTM lung infection.[1,2] All patients were on a stable, guideline-based multidrug regimen which was continued throughout the trial.[1,2] The randomized phase was followed by a 12-week open-label extension study.[1,2] Patients characteristics were generally similar between groups for mean age, gender, race, BMI, percent predicted mean forced expiratory volume in one second (FEV_1),

presence of disease and type of microorganism (see **Table 5**). [1,2] Only adults with pulmonary nontuberculous mycobacteria with evidence of nodular bronchiectasis and/or cavitary disease by chest computed tomography (CT) and a chronic MAC or *M. abscessus* infection were included.[1,2] Patients with clinically significant cardiac, pulmonary, hepatic, or renal disease were excluded, however, no definition for clinical significance was given.[1,2] Full inclusion and exclusion criteria may be found in **Table 5.**

The primary endpoint was change from baseline on a semi-quantitative scale (SQS) for mycobacterial culture growth in the ALIS plus GBT group at day 84 compared to placebo plus GBT within the same timeframe. [1,2] SQS is a 7-step reporting method that has been used to evaluate mycobacterial burden observed from culture samples.[1,16] However, the FDA reviewer noted that the primary endpoint of mycobacterial density assessed by the SQS had unclear clinical relevance as this tool had not been used in previous NTM studies.[2] The data are limited whether SQS is predictive of clinical response to therapy or if it correlates with subjective measures of response such as symptom improvement or changes radiographic appearance.[16] Media were examined for the presence and number of mycobacterial culture colonies then given a categorical result that ranged from step 1 (culture negative; 0 colonies; no liquid medium growth) to step 7 ("4+"; >500 colonies; positive liquid medium growth observed). [1,2] At baseline, there were a higher percentage of patients evaluated at step 3 in the ALIS group compared to placebo (39% vs. 22%, respectively), but fewer ALIS subjects at step 7 compared to the placebo group (32% vs. 42%).[1,2] Roughly 11% of subjects in both groups were culture negative at baseline. [1,2] The clinically relevant secondary and tertiary endpoints were proportion of subjects with NTM negative culture at Day 84 and change in the six-minute walk test (6MWT) distance, respectively. [1,2] The 6MWT is a self-paced test of walking capability where patients are asked to walk on a flat surface for as long as possible in a 6-minute timeframe and distance in meters is documented.[17]

Study 112 outcomes were analyzed with modified intention-to-treat (mITT) population defined as all randomized patients given one dose or more amikacin LIS.[1,2] At day 84, there was not a statistically significant difference in SQS change from baseline in ALIS-treated patients compared to placebo (52.3% vs. 51.1%, respectively; p=0.072). [1,2] A greater proportion of subjects in the ALIS group achieved one negative culture reading compared to placebo at 84 days (32% vs. 9%, respectively; p=0.0057), and there was a statistically significant difference in change from baseline in 6MWT distance at day 84 that favored the ALIS group compared to placebo (20.6 m increase vs. 25 m decrease, respectively; p=0.0102). [1,2]

Study 212 was a 6-month, phase 3, randomized, open-label, multicenter trial of ALIS in adult patients (N=336) with refractory MAC lung disease.[2,3] Subjects were considered to have refractory MAC lung disease if they had a positive sputum culture after at least 6 months of treatment with guideline-based, optimized background regimen (OBR) of 3 antibiotics. [2,3] Patients were excluded for comorbidities including cystic fibrosis, active pulmonary tuberculosis, immunodeficiency syndromes, amikacin resistance, or active malignancy. [2,3] Full inclusion and exclusion criteria may be found in the evidence table (**Table 5**). Patients were stratified by smoking status at screening; most were not current smokers (89%) and many had bronchiectasis (62.5%).[2,3] Patients who met criteria were randomized 2:1 to either ALIS plus OBR (n=224) or OBR alone (n=112). [2,3] Baseline characteristics were generally similar except for a larger percentage of females in the ALIS plus OBR group compared to OBR alone (73.7% vs. 60.7%, respectively). [2,3] Most of the patients were from the United States (42%), white (70%), and were on OBR at screening (>90%).[2,3] The OBR regimens typically included a macrolide, a rifamycin, and ethambutol. [2,3] Specific doses were not reported. Concomitant use of other medication combinations and antibacterial agents were allowed during the trial as well as rescue medications which are highlighted in **Table 5.**

The surrogate primary endpoint was proportion of patients with negative sputum culture conversion based on monthly assessments from baseline to month 6.[2,3] Secondary endpoints included change from baseline in the 6-minute walk test (6MWT) at 6 months and change from baseline in the St George's Respiratory Questionnaire (SGRQ). [2,3] The SRGQ is a 76-item questionnaire that assesses health-related quality of life (HRQOL) in respiratory disease with a minimum score

of 0 (no effect on HRQOL) maximum score of 100 (maximum perceived distress).[18] Some studies have suggested a minimal clinically important difference (MCID) on the SGRQ to be 4 units.[18]

There was a statistically significant greater proportion of patients with a negative sputum culture conversion by month 6 in the ALIS plus OBR group compared to the OBR group alone (29.0% vs. 8.9%, respectively, P<0.0001). [2,3] After a sensitivity analysis was performed there were 3 subjects in each group who did not demonstrate sustained sputum culture conversion. [2,3] The long-term clinical significance of a sputum culture conversion by month 6 is unclear. There was not a statistically significant difference between groups in the 6MWT or the SGRQ by month 6. [2,3]

Study 312 was an open label extension of study 212 to assess the safety and tolerability of ALIS 590 mg plus GBT in MAC lung disease in patients who were refractory to conventional therapy. [2,3] The study enrolled patients who successfully completed the 6-month and end of treatment visit and had not achieved culture conversion in either group. [2,3] The results are reported in the clinical safety section below.

Several limitations of the trial design present challenges to determine the true clinical benefit of ALIS. Amikacin LIS was used as add-on therapy to a guideline-based background treatment but it was unclear if the background regimen drugs and doses were optimized for all participants, especially those with co-morbidities. In study 212, a higher percentage of comorbidities at baseline was observed in the OBR alone arm which included COPD (33% in OBR alone arm vs. 22.4% in ALIS+OBR arm), pulmonary cavitation (17% in OBR alone arm vs. 12% in ALIS+OBR arm), and dyspnea (13% OBR alone arm vs. 8% in ALIS+OBR arm). [2-4] The impact of the baseline group imbalance on efficacy and safety outcomes is unclear. For many patients, especially with nodular-bronchiectatic MAC pulmonary disease, sustained mycobacterial eradication may not be achievable and post-treatment relapses are common. Therefore, it is unclear whether antibiotic therapy duration is an adequate marker for treatment success. In Study 212, patients who did not convert to negative sputum culture at month 6 were discontinued from the study or crossed over to ALIS therapy at month 8, so there is no clear evidence to evaluate comparative efficacy beyond 6 months. A negative culture conversion does not necessarily translate into meaningful clinical improvements in physical function or health-related quality of life. Clinically relevant outcomes such as improvements in the 6MWT reported in Study 112 were not replicated in Study 212. The FDA reviewer could not determine the reasons for the discordance in the 6MWT and suggested the possibility of a chance finding.

Clinical Safety:

In all combined clinical studies with multiple amikacin LIS exposures, 646 (80.5%) patients received the FDA-approved 590 mg dose.[2,4] The exposure duration ranged from 3-20 months. [2,4] There were 32 deaths reported in the development of ALIS, and all except one occurred in studies 112, 212, and 312. [2,4] However, there was no apparent imbalance in mortality between ALIS plus OBR and OBR groups. [2,4] Roughly one-quarter to one-third of patients in the ALIS group discontinued therapy prematurely and, compared to the OBR group, most of the discontinuations were due to adverse events (16-17% vs 0-1%, respectively). [2,4] In study 212, many of the treatment emergent adverse effects (TEAEs) in the ALIS group were due to pulmonary and airway disorders (**see Table 3**). [2,4] Pre-defined adverse events of interest in the ALIS + OBR group which led to the discontinuations included bronchospasm (n=9), dysphonia (n=5), exacerbation of underlying lung disease (n=4), ototoxicity (n=4), allergic alveolitis/hypersensitivity pneumonitis (n=3), cough (n=2), hemoptysis (n=2), pneumonia (n=1) and upper airway irritation (n=1). [2-4]

Table 3. Treatment Emergent Adverse Events in Study 212 in >5% of Amikacin + OBR Treated Patients Compared to OBR Alone[2-4]

	Amikacin LIS + OBR N=223 (%)	OBR N=112 (%)
Dysphonia	105 (47.1)	1 (0.9)
Cough	87 (39)	20 (17.9)
Dyspnea	48 (21.5)	10 (8.9)
Upper airway inflammation	40 (17.9)	2 (1.8)
Hemoptysis	40 (17.9)	14 (12.5)
Musculoskeletal pain	39 (17.5)	12 (10.7)
Fatigue and asthenia	36 (16.1)	11 (9.8)
Diarrhea	29 (13)	5 (4.5)
Nausea	26 (11.7)	4 (3.6)
Headache	22 (9.9)	5 (4.5)
COPD exacerbation	19 (8.5)	4 (3.6)
Tinnitus	17 (7.6)	1 (0.9)
Wheezing	16 (7.2)	2 (1.8)
Pyrexia	16 (7.2)	5 (4.5)
Rash	15 (6.7)	1 (0.9)
Vomiting	15 (6.7)	4 (3.6)
Weight decreased	14 (6.3)	1 (0.9)
Decreased appetite	14 (6.3)	8 (7.1)
Dizziness	14 (6.3)	3 (2.7)
Sputum change	13 (5.8)	1 (0.9)
Chest discomfort	12 (5.4)	3 (2.7)

Study 312 was an open-label extension study of Study 212 and provided limited safety evidence and no comparative efficacy data. [2-4] There were similar rates for discontinuations between groups. However, for ALIS new-starts, discontinuations due to adverse events accounted for 11 of the 15 discontinuations (73%), while discontinuation due withdrawal by subject (5/13) and discontinuation due to lack of efficacy (3/13) were the main reasons for discontinuation for those that were continued on ALIS. [2-4] Within the first 4-6 weeks after initiation, new start ALIS patients experienced a significantly higher incidence of dysphonia, cough, dyspnea and upper airway irritation than those continuing ALIS therapy.

Due to these significant adverse events experienced in clinical trials, ALIS has a FDA Boxed Warning for increased risk of, hypersensitivity pneumonitis, hemoptysis, bronchospasm, and exacerbation of underlying pulmonary disease that have led to hospitalizations in some cases. [2,4] Additional warnings and precautions include ototoxicity, nephrotoxicity, neuromuscular blockade, and embryo-fetal toxicity. [2,4]

The safety of ALIS has not been evaluated in pregnancy, breastfeeding women, pediatric patients, or patients with hepatic or renal impairment. [2,4]

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Improved survival
2) Improvement of MAC symptoms or functional capacity
3) Prevention of MAC pulmonary complications
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Change from baseline to day 84 in the semi-quantitative scale (SQS) for mycobacterial growth
2) Sputum culture conversion based on assessment of monthly sputum cultures from baseline to month 6

Table 4. Pharmacology and Pharmacokinetic Properties. [2,4]

Parameter	
Mechanism of Action	Disruption and inhibition of protein synthesis in the target bacteria by binding to the 30S ribosomal subunit.
Oral Bioavailability	Variable (Inhalation); average expected absorption is 7.42% of dose
Distribution and Protein Binding	368.6 L; ≤10% protein binding
Elimination	Renal via glomerular filtration (>90% unchanged drug in urine)
Half-Life	5.9 to 19.5 hours
Metabolism	No appreciable metabolism

Table 5. Comparative Evidence Table.[1-4]

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Oliver, et al. 2016 (Study 112) Phase 2, RCT, DB, PC followed by open-label extension phase	1. ALIS 590 mg inhalation once daily 2. placebo (sterile lipid carrier suspension) inhalation once daily 84 days randomized + 84 days open label	Demographics: Mean age: 58.5 years Race: 90-95% white Female: 88% BMI: 22 kg/m^2 Mean FEV1%: 63% Predominantly MAC: 64% CF: 19% Key Inclusion Criteria: -Adult patients with PNTM disease as defined by ATS/IDSA -Received ATS/IDSA GBT for at least 6 months prior -Persistent positive cultures for MAC or *M. abscessus* Key Exclusion Criteria: -Current smoker -FEV1 < 30% of predicted -Clinically significant cardiac, pulmonary, hepatic, or renal disease -Systemic immune deficiency -Malignancy -Hx of daily continuous oxygen supplementation	ITT: 1. 44 2. 46 mITT: 1. 44 2. 45 Attrition: 1. 9 (20.5%) 2. 0 (0%) 19 D/C study drug during open label extension phase	Primary Endpoint: Change from baseline to EOT (day 84) on SQS mycobacterial growth scale 1. 52.3% 2. 51.1% P=0.072 Secondary Endpoints: Proportion of subjects with negative sputum culture for NTM at day 84 1. 14 (32%) 2. 4 (9%) P=0.006 Tertiary Endpoints Change from baseline to day 84 in the 6MWT 1. 20.6 m 2. -25.0 m Difference: 45m P=0.0102	NS 23%/5 N/A	Deaths: 1. 4 2. 5 D/C due to AE: 1. 9 (20.5%) 2. 0 (0%) - Infective exacerbations of underlying pulmonary disease and dyspnea 1. 7/9 (78%) 2. 0 (0%) TEAEs 1. 22 (50%) 2. 10 (22.2%) SAEs 1. 8 (18.2%) 2. 4 (8.9%) -infection and infestation 1. 11.4% 2. 6.7%	N/A for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear. Method of randomization/allocation not described; groups unbalanced in baseline mycobacterial load; higher percentage of females in the ALIS group (74%) compared to placebo (61%) Performance Bias: Unclear. Double blinded but no details how maintained; empty liposome placebo delivered with customized investigational nebulizer Detection Bias: Unclear. No details how/if assessors were blinded Attrition Bias: High. Greater loss in ALIS group; mITT used for analysis Reporting Bias: High. Reported endpoints that were not prespecified such as durability of sputum culture at 12 months Other Bias: Unclear. Sponsored by Insmed; multiple authors were consultants/employees of sponsor; medical writing assistance by Insmed employees **Applicability**: Patient: Subjects with refractory MAC or *M. abscessus* lung infections and included subjects with cystic fibrosis; median duration of MAC lung disease (4.5 vs. 3.3 years) Intervention: ALIS 590 mg dose likely appropriate based on prior pharmacologic studies Comparator: Placebo + GBT was appropriate for efficacy Outcomes: Surrogate endpoint with unclear link to clinical outcomes Setting: 18 US sites and 1 Canada site

2. Griffith, et al. 2018 (Study 212) Phase 3, OL, RCT	1. ALIS 590 mg once daily + OBR 2. OBR	Demographics: Mean age: 64 years old Female: 70% 1. 73.7% 2. 60.7 Multidrug regimen at screening: 90% Current smoker: 1. 11.6% 2. 8.9% Concomitant medications: Selective beta-2 receptor agonists: 1. 52.2% 2. 38.4% Fluoroquinolones: 1. 27.2% 2. 36.6% Glucocorticoids: 1. 27.7% 2. 18.8% Key Inclusion Criteria: - Age: ≥18 years - positive for NTM MAC lung infection documented by 2 cultures after 6 months of multi-drug tx - MAC-positive sputum at screening Key Exclusion Criteria: - CF, active TB, amikacin resistance, Hx of lung transplant - immunodeficiency syndromes, active malignancy, chronic steroid or anti-inflammatory therapy last 28 days - pregnancy - alcohol/substance abuse - hearing loss/or dysfunction where risk of AG toxicity outweighs the benefit - AST/ALT ≥3 x ULN, total bili ≥ 2 times ULN at screening, ANC ≤500/µL, Scr >2 x ULN - any condition that interferes with ability to safely complete study	ITT: 1. 224 2. 112 Attrition: 1. 75 (33.5%) 2. 9 (8%)	Primary Endpoint: Sputum culture conversion based on assessment of monthly sputum cultures from baseline to month 6. Converter ALIS + OBR: 65 (29%) OBR alone: 10 (8.9%) Non-converter ALIS + OBR: 159 (71%) OBR alone: 102 (91.1%) P<0.0001 Secondary Endpoint: Change from baseline in 6MWT distance at month 6 LSMD: -3.0 (95% CI, -20.6 to 14.7) P = 0.7223 Change from baseline SGRQ score: 1. 4.2 2. 0.4 LSMD: 3.8 (95% CI, 0.7 to 6.9) P = 0.0177	 20.1%/5 NS NS	Death 1. 9 (4%) 2. 5 (4.5%) D/C due to AE: 1. 39 (17.4%) 2. 1 (1%) TEAEs 1. 219 (98.2%) 2. 101 (90.2%) SAEs 1. 45 (20.2%) 2. 18 (16.1%) Subject Count of Unplanned Hospitalizations 1. 41 (18.4%) 2. 15 (13.4%) Hospitalization reasons: -Exacerbation of underlying pulmonary disease 1. 22/82 (27%) 2. 5/23 (22%) - Lower RTIs 1. 22/82 (27%) 2. 4/23 (17%)	N/A for all	**Risk of Bias (low/high/unclear)**: Selection Bias: High. Open label; no matching placebo; interactive web response system used for randomization; patients could be excluded for any condition deemed to interfere with study outcomes Performance Bias: High. Investigators, patients not blinded to treatment. Detection Bias: High. Open label, no placebo. Data were collected by the investigators and analyzed by the sponsor. Attrition Bias: High. One-third of study population discontinued treatment mostly due to adverse effects Reporting Bias: Low. Outcomes reported as prespecified Other Bias: Unclear. Study authors received grants, personal fees, and/or consulting support from manufacturer. **Applicability**: Patient: Applies only to MAC positive patients refractory to multi-drug treatment after 6 months; extensive trial exclusions Intervention: ALIS 590 mg dose likely appropriate based on prior pharmacologic studies Comparator: Optimized background regimen (no active comparator); would have been appropriate to have placebo delivery component Outcomes: Surrogate endpoint with unclear link to clinical outcomes; tools used in the efficacy assessments (SGRQ, 6MWT) have been validated, but have not been validated in the MAC population. Setting: 127 sites in 18 countries

Abbreviations: 6MWT = six minute walk test; AG = aminoglycoside; ALIS = amikacin liposome inhalation suspension; ALT = alanine transaminase; ANC = absolute neutrophil count; ARR = absolute risk reduction; AST = aspartate aminotransferase; CI = confidence interval; CF = cystic fibrosis; DB = double blind; D/C = discontinue; EOT = end of treatment; GBT = guideline-based therapy; Hx = history; ITT = intention to treat; LSM = least squares mean; LSMD = least squares mean difference; MAC = mycobacterium avian complex; mITT = modified intention to treat; N = number of subjects; NA = not applicable;

NNH = number needed to harm; NNT = number needed to treat; NS = nonsignificant; NTM = nontuberculous MAC; OBR = optimized background regimen; OL = open label; PC = placebo controlled; PNTM = pulmonary nontuberculous mycobacteria; PP = per protocol; RTI = respiratory tract infection; SGRQ = St George's Respiratory Questionnaire; SQS = semi-quantitative scale; TB = tuberculosis; tx = treatment; ULN = upper limit of normal

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Appendix 1: Prescribing Information Highlights

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

ARIKAYCE® (amikacin liposome inhalation suspension), for oral inhalation use
Initial U.S. Approval: 2018
LIMITED POPULATION

WARNING: RISK OF INCREASED RESPIRATORY ADVERSE REACTIONS
See full prescribing information for complete boxed warning.

ARIKAYCE has been associated with a risk of increased respiratory adverse reactions, including, hypersensitivity pneumonitis, hemoptysis, bronchospasm, and exacerbation of underlying pulmonary disease that have led to hospitalizations in some cases. (5.1, 5.2, 5.3, 5.4)

----------INDICATIONS AND USAGE----------
LIMITED POPULATION: ARIKAYCE is an aminoglycoside antibacterial indicated in adults who have limited or no alternative treatment options, for the treatment of *Mycobacterium avium* complex (MAC) lung disease as part of a combination antibacterial drug regimen in patients who do not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy. As only limited clinical safety and effectiveness data for ARIKAYCE are currently available, reserve ARIKAYCE for use in adults who have limited or no alternative treatment options. This drug is indicated for use in a limited and specific population of patients. (1)

This indication is approved under accelerated approval based on achieving sputum culture conversion (defined as 3 consecutive negative monthly sputum cultures) by Month 6. Clinical benefit has not yet been established. (1)

Limitation of Use:
ARIKAYCE has only been studied in patients with refractory MAC lung disease defined as patients who did not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy. The use of ARIKAYCE is not recommended for patients with non-refractory MAC lung disease.

----------DOSAGE AND ADMINISTRATION----------
- For oral inhalation use only. (2.1)
- Use ARIKAYCE vials only with the Lamira Nebulizer System. (2.1)
- The recommended dosage in adults is once daily oral inhalation of the contents of one 590 mg/8.4 mL ARIKAYCE vial. (2.2)
- Pre-treatment with inhaled bronchodilator should be considered in patients with a history of hyperreactive airway disease. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
ARIKAYCE is supplied as a sterile, aqueous, liposome suspension for oral inhalation in a unit-dose glass vial containing amikacin 590 mg/8.4 mL. (3)

----------CONTRAINDICATIONS----------
ARIKAYCE is contraindicated in patients with a known hypersensitivity to any aminoglycoside. (4)

----------WARNINGS AND PRECAUTIONS----------
- Hypersensitivity Pneumonitis: Reported with ARIKAYCE treatment; if hypersensitivity pneumonitis occurs, discontinue ARIKAYCE and manage patients as medically appropriate. (5.1)
- Hemoptysis: Higher frequency of hemoptysis has been reported with ARIKAYCE treatment. If hemoptysis occurs, manage the patients as medically appropriate. (5.2)
- Bronchospasm: Higher frequency of bronchospasm has been reported with ARIKAYCE treatment. Treat patients as medically appropriate if this occurs during treatment with ARIKAYCE. (5.3)
- Exacerbations of Underlying Pulmonary Disease: Higher frequency of exacerbations of underlying pulmonary disease has been reported with ARIKAYCE treatment. Treat patients as medically appropriate if this occurs during treatment with ARIKAYCE. (5.4)
- Ototoxicity: Higher frequency of ototoxicity has been reported with ARIKAYCE treatment. Closely monitor patients with known or suspected auditory or vestibular dysfunction. If patients develop tinnitus this may be an early symptom of ototoxicity. (5.5)
- Nephrotoxicity: Aminoglycosides can cause nephrotoxicity. Close monitoring of patients with known or suspected renal dysfunction may be needed when prescribing ARIKAYCE. (5.6)
- Neuromuscular Blockade: Aminoglycosides may aggravate muscle weakness because of a potential curare-like effect on neuromuscular function. If neuromuscular blockade occurs, it may be reversed by the administration of calcium salts but mechanical assistance may be necessary .(5.7)
- Embryo-Fetal Toxicity: Aminoglycosides can cause total, irreversible, bilateral congenital deafness in pediatric patients exposed in utero. (5.8, 8.1)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence ≥10% and higher than control) in the patients with refractory MAC lung disease were: dysphonia, cough, bronchospasm, hemoptysis, ototoxicity, upper airway irritation, musculoskeletal pain, fatigue/asthenia and exacerbation of underlying pulmonary disease, diarrhea, and nausea. (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Insmed Incorporated at 1-844-4-INSMED or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 9/2018

Amikacin Liposome Inhalation Suspension

Goal(s):

- Limit the use of amikacin liposome inhalation suspension to adult patients with limited or no alternative treatment options, for the treatment of Mycobacterium avium complex (MAC) lung disease as part of a combination antibacterial drug regimen in patients who do not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy.

Length of Authorization:

- 6-month initial approval; Up to 12 months renewal

Requires PA:

- Amikacin Liposome Inhalation Suspension (ALIS)

Covered Alternatives:

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

Approval Criteria		
1. Is this a request for continuation of therapy previously approved by the FFS program?	**Yes**: Go to **Renewal Criteria**	**No**: Go to #2
2. Is this request for treatment of an adult ≥18 years of age with Mycobacterium avium complex (MAC) lung disease verified through sputum culture?	**Yes:** Record ICD10 code. Go to #3.	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is this agent being prescribed by or in consultation with an infectious disease specialist, pulmonologist, or a specialist in the treatment of MAC lung infections?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.

Approval Criteria		
4. Has the patient been adherent to a 6-month course of a guideline-based 3-drug antibacterial treatment regimen including a macrolide, a rifamycin, and ethambutol within the last year?	**Yes:** List the antibiotic regimen. Go to # 5	**No:** Pass to RPh. Deny; medical appropriateness. 6-month trial of guideline-based, 3-drug antibacterial regimen is required before starting amikacin liposome inhalation suspension.
5. Will the patient be using amikacin liposome inhalation suspension as add on therapy to a guideline-based, 3-drug antibacterial MAC treatment regimen as described in question #4?	**Yes:** Approve for **6 months.** Dose not to exceed 1 vial per day (590 mg/8.4 ml vial). Renewal consideration will require documentation of monthly MAC sputum cultures and regimen adherence.	**No:** Pass to RPh. Deny; medical appropriateness. Concurrent guideline-based, 3-drug antibacterial MAC regimen is required per product labeling.

Renewal Criteria		
1. Has the patient experienced evidence of respiratory adverse effects since treatment initiation such as hypersensitivity pneumonitis, hemoptysis, bronchospasm, or exacerbation of underlying pulmonary disease?	**Yes**: Pass to RPh. Deny; medical appropriateness.	**No**: Go to #2
2. Has the patient been adherent to both amikacin LIS and guideline-based background MAC antibiotic regimen?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
3. Is there documentation of at least 3 consecutive negative monthly sputum cultures in the first 6 months of amikacin LIS therapy or a minimum of 2 consecutive negative monthly sputum cultures in the last 2 months of amikacin LIS therapy?	**Yes**: Document results of sputum culture. Approve for additional 3 months. Therapy not to exceed 12 months after converting to negative sputum status (≥3 consecutive negative MAC cultures).	**No:** Pass to RPh. Deny; medical appropriateness.

P&T/DUR Review: 11/19 (DE)
Implementation: TBD

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Drug Class Review: Targeted Therapies for Gaucher Disease

Date of Review: November 2019 **End Date of Literature Search:** 04/12/19

Purpose for Class Review: To evaluate evidence of efficacy and safety for current pharmacological treatments for Gaucher Disease.

Research Questions:

1. What is the efficacy or effectiveness of pharmacological treatments for Gaucher Disease compared to placebo or other pharmacotherapy?
2. Is there any evidence that pharmacological treatments for Gaucher Disease differ in harms?
3. Are there specific subpopulations for which one agent is better tolerated or more effective than other therapies?

Conclusions:

- There is low quality evidence of no difference in hemoglobin concentration, platelet count, liver volume or spleen volume for imiglucerase compared to velaglucerase alfa in patients with symptomatic Type 1 Gaucher disease.[1,2] Evidence is limited by small study populations, lack of comparator groups, and open-label study designs.[1,2]
- There is insufficient direct comparative evidence for taliglucerase alfa, but placebo comparisons demonstrate improvements in hemoglobin levels (MD 1.4 to 2.2 g/dL), spleen volume (MD -27% to -41%), and liver volume (MD -6.3% to -4.1%) with inconsistent evidence for improved platelet counts.[3] It is unclear whether these differences correlate with improved clinical outcomes for patients with Type 1 Gaucher disease, and there are insufficient data from RCTs on long-term outcomes including quality of life, disease progression, or mortality.
- There is low quality evidence from a single non-inferiority trial that patients switching from imiglucerase to eliglustat maintain disease stability compared to continued treatment with imiglucerase (84.8% vs. 93.6%, respectively).[4] Compared to placebo at 39 weeks, there was low quality evidence of statistically significant differences with eliglustat treatment in all laboratory markers including reduction in spleen volume (mean difference [MD] 30%, 95% CI 36.82 to 23.24; p<0.001), liver volume (MD −6.64%, 95% CI −11.37 to −1.91; p=0.0072), hemoglobin level (MD 1.22 g/dL, 95% CI 0.57 to 1.88; p=0.0006), and platelet count (MD 41.06%, 95% CI 23.95 to 58.17; p<0.0001).[4] There were no differences in bone disease or symptom improvement at 39 weeks, but data are limited by a short study duration and inclusion of patients with only mild bone-related symptoms at baseline (mean lumbar spine bone mineral density T-score of -1.1).[5] Eliglustat is primarily metabolized by P450 enzymes and requires CYP2D6 testing to determine metabolizer status and appropriate dose.[6]
- Trials evaluating miglustat and imiglucerase as monotherapy or combination therapy demonstrated no difference in laboratory markers in patients previously stable on enzyme replacement therapy (ERT).[1,2] Food and Drug Administration (FDA) labeling for miglustat recommends it as a second-line option only for patients who are unable to receive ERT.[7]
- There is insufficient data from RCTs to evaluate clinical bone-related outcomes, mortality, or quality of life in patients with Type 1 Gaucher disease.
- There is insufficient evidence to support combination treatment with targeted therapies for Gaucher disease.
- There is insufficient evidence of efficacy or safety in patients with Type 2 or Type 3 Gaucher disease.

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Recommendations:

- Create a class for lysosomal storage disorders and designate miglustat as non-preferred based on FDA labeling as second-line therapy and eliglustat as non-preferred based on need for additional enzymatic testing.
- Designate at least one ERT for Gaucher disease as a preferred product. Evaluate comparative costs in executive session.
- Recommend prior authorization criteria for all targeted therapies for Gaucher disease to ensure medically appropriate use.

Background:

Gaucher disease is an inherited, autosomal recessive lysosomal storage disorder. Affected patients have homozygous mutations in the glucocerebrosidase gene (GBA).[8] Over 200 mutations in the GBA gene have been documented, though not all mutations are associated with severe disease or a clinical phenotype. While genotype does not directly correlate to a clinical phenotype, the most common variants include N370S alleles which are associated more commonly with bone involvement and a homozygous L444P genotype which is usually associated with more severe neurologic disease.[8] Mutations in GBA lead to a nonfunctional GBA enzyme and accumulation of glucosylceramide in macrophage cells.[8] These cells, referred to as Gaucher cells, can infiltrate organs including the bone, spleen, and liver leading to displacement of normal cells in the bone marrow, bone marrow expansion, altered vascularity, and tissue death or necrosis.[8] In other tissues, Gaucher cells can cause fibrosis, necrosis, and scarring. Approximately 5% of patients also exhibit neurologic impairment, though the exact etiology for central nervous system (CNS) involvement is unknown.[8]

The rate of disease progression is highly variable, and diagnosis can occur at any age. The disease is classified into primarily 3 types based on clinical presentation. Type 1 is characterized by bone disease and lack of neurologic involvement and accounts for more than 90% of patients.[2,8] Type 2 is associated with severe CNS symptoms and is typically associated with early disease onset, rapid progression, and death by the age of 4 years.[8] The Type 3 is associated with both bone and CNS involvement and is typically less severe than Type 2.[8] Common signs and symptoms of bone involvement include splenomegaly, hepatomegaly, bone pain, radiologic bone disease, growth retardation, thrombocytopenia, and anemia.[2,8] Neurologic symptoms can manifest as a wide variety of symptoms. In patients with Type 2 disease, typical neurologic symptoms include neck and trunk rigidity, oculomotor paralysis, and bulbar involvement (particularly swallowing disorders).[8] Other neurologic symptoms may include progressive myoclonic epilepsy, ataxia, spasticity, delayed psychomotor development, or dementia.[8] Build-up of Gaucher cells in tissue eventually may lead to irreversible fibrosis in the lung, spleen, liver, bone or other tissues. Long-term complications may include osteoarthritis, bone fractures, liver fibrosis, neurologic complications, splenic infarct or rupture, and pulmonary fibrosis.[8] Patients with Gaucher disease also have a higher risk of cancer, particularly multiple myeloma, and Parkinson's disease compared to the general population.[2,8]

Diagnosis of Gaucher disease is typically confirmed by biochemical testing for GBA enzyme activity though molecular genetic testing may be performed to confirm the diagnosis or for prenatal and carrier testing.[8] The estimated prevalence of Gaucher disease is approximately 1 in 40,000 to 60,000 births in the general population, but incidence is much more common in people of Ashkenazi Jewish descent.[2,8] In Oregon, newborn screening currently includes testing for enzymatic activity of GBA, and Gaucher disease is listed on Line 60 of the Health Evidence Review Commission prioritized list. In the Oregon Health Plan (OHP) fee-for service (FFS) population, only one or two patients have claims indicating a diagnosis of Gaucher disease.

Pharmacological treatment is the current standard of care for all patients with symptomatic Type 1 Gaucher disease.[8] The first treatments for Gaucher disease (alglucerase and imiglucerase) were FDA approved in 1991, and currently available therapies include intravenous ERT or oral substrate reduction therapies (**Table 1**). In asymptomatic patients, ongoing monitoring is recommended, and molecular screening may help predict clinical course and inform frequency of monitoring. Because administered ERT does not cross the blood brain barrier, there is little impact on neurologic manifestations of Gaucher disease, and the

limited available evidence does not demonstrate any consistent benefit for patients with neurologic symptoms. Therefore, therapy for Type 2 Gaucher disease is primarily focused on supportive care, and the role of pharmacological treatment in Type 3 disease is unclear.[2,8]

Table 1. Indications and Dosing.[9]

Generic Name (Brand)	Indication(s)	Strength/Route	Dose and Frequency
Enzyme Replacement Therapies			
Imiglucerase (Cerezyme®)	Type 1 Gaucher disease complicated by anemia, thrombocytopenia, bone disease, hepatomegaly, or splenomegaly	400 units IV powder for solution	Initial dosages of 2.5 units/kg 3 times weekly to 60 units/kg once every 2 weeks. Infused over 1-2 hours with dosage individualized to each patient.
Taliglucerase alfa (Elelyso®)	Type 1 Gaucher disease	200 units IV powder for solution	60 units/kg over 1-2 hours every 2 weeks
Velaglucerase alfa (Vpriv®)	Type 1 Gaucher disease	400 units IV powder for solution	60 units/kg over 1 hour every 2 weeks
Substrate Reduction Therapies			
Eliglustat (Cerdelga)	Type 1 Gaucher disease in adults who are not ultra-rapid CYP2D6 metabolizers as detected by an FDA-cleared test	84 mg oral capsule	84 mg BID (extensive or intermediate CYP2D6 metabolizers) 84 mg QD (poor CYP2D6 metabolizers)
Miglustat (Zavesca®)	Mild/moderate Type 1 Gaucher disease in adults for whom ERT is not an option (monotherapy only)	100 mg oral capsule	100 mg TID

Abbreviations: BID = twice daily; ERT = enzyme replacement therapy; FDA = Food and Drug Administration; IV = intravenous; QD = once daily; TID = three times daily

Clinically relevant outcomes for patients with Gaucher disease include symptom improvement (particularly bone pain and fatigue), improved health-related quality of life, slowed disease progression, and prevention of long-term complications such as clinical bone-related events (e.g., bone crisis, fractures, and ischemic bone events), Parkinson's disease and cancer.[10] However, clinical trials primarily focus on assessments of spleen and liver volume, platelet count and hemoglobin level. While hepatomegaly and splenomegaly are often associated with pathologic disease, there is no minimum difference in size which is associated with symptom improvement. In 2018, the European Working Group on Gaucher disease conducted a literature review and a patient survey to assist in the establishment of more specific short and long-term treatment goals.[10] Due to the rarity of the condition, there is limited evidence available on specific goals of treatment, and the majority of recommendations were made were based on expert consensus opinion from 35 providers.[10] Short-term treatment goals for objective laboratory markers which achieved consensus from experts are listed in **Table 2**, though the recommendations are limited as the majority of voting participants had conflicts of interest from industry which may increases risk of bias.[10] General recommendations were also made to improve quality of life, fatigue, function, and bone pain with assessments from validated scoring tools. No consensus was reached on treatment goals for other disease biomarkers or disease severity scores due to insufficient evidence and inadequate validation of these surrogate outcomes.[10]

Current data from RCTs evaluating pharmacological treatment are limited to durations of one to two years, though extension studies have demonstrated continued stability of spleen and liver volume, platelet count and hemoglobin level after 2 to 8 years of treatment in patients with Type 1 Gaucher disease.[6,7,11-13] While there are multiple long-term analyses of international registry and observational studies which evaluate efficacy outcomes before and after the introduction of ERT,[13-18] the long-term impact of pharmacological therapy on disease progression or long-term complications remains unclear due to methodological limitations in the available observational data and lack of consistently documented disease progression before the availability of ERT.[4]

A summary of relevant drug information is available in **Appendix 1**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, warnings and precautions.

Table 2. Select short-term treatment goals for patients with Type 1 Gaucher disease based on expert consensus opinion (modified)[10]

Category	Management Goal
Hemoglobin	Increase hemoglobin levels within 12 to 24 months to >11.0 g/dL for women and children and >12.0 g/dL for men
Platelet Count	Increase platelet counts during the first year of treatment sufficiently to prevent surgical, obstetrical, and spontaneous bleeding - In patients with splenectomy: normalization of platelet count by 1 year of treatment - In patients with an intact spleen: achieve platelet count of ≥100,000/mm^3 by 3 years of treatment
Bone Mineral Density	Increase bone mineral density by 2 years in adults for patients with a T-score below −2.5 at baseline Attain normal or ideal peak skeletal mass in children Normalize growth such that the height of the patient is in line with target height, based upon population standards and parental height, within 2 years of treatment
Splenomegaly	Reduce spleen volume to <2 to 8 times normal (or in absence of volume measurement tools reduce spleen size) by year 1–2, depending on baseline spleen volume
Hepatomegaly	Reduce the liver volume to 1.0 to 1.5 times normal (or in absence of volume measurement tools aim for normal liver size) by year 1–2, depending on baseline liver volume

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

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

Systematic Reviews:
A Cochrane review published in 2015 evaluated the evidence of safety and efficacy for pharmacologic treatments for Gaucher disease.[2] Four included trials evaluated treatment naïve patients and 4 trials evaluated switching therapy in patients already on treatment.[2] The majority of included studies included adults with average ages ranging from 25 to over 50 years. Three studies included children though the total included population was small. Patients with stable disease were defined as having received ERT for at least 2 years. Five of the 8 included studies had high or unclear risk for selection or performance bias due to inadequate randomization, allocation concealment, or blinding.[2] Two trials had incomplete outcome reporting.[2] Comparisons included same drug dose-comparisons, imiglucerase versus aliglucerase, imiglucerase versus velaglucerase alfa, and imiglucerase versus miglustat. Trial durations ranged from 6 to 24 months.[2] The primary outcome was frequency of adverse events, and safety assessment for ERT included 234 patients.[2] Many common adverse events were classified as infusion-related and were mild, moderate, or transient. Serious adverse events were reported in 19 patients treated with imiglucerase (primarily

associated with worsening disease progression), 3 patients treated with velaglucerase alfa (allergic dermatitis, prolonged aPTT, and seizure), and 2 patients treated with taliglucerase alfa (hypersensitivity reactions).[2] In treatment naïve patients, there was no statistical difference in hemoglobin concentration, platelet count, liver volume, or spleen volume for various ERT products.[2] There was also no difference in treatment outcomes based on dose or frequency for patients with a history of stable disease when evaluating different dosing regimens of velaglucerase alfa, taliglucerase alfa, or imiglucerase.[2] There was insufficient data to evaluate bone-related outcomes for ERT. Two studies evaluated miglustat in combination with ERT compared to monotherapy in patients with Type 1 (n=36) or Type 3 (n=30) Gaucher disease.[2] The most common adverse events associated with treatment were gastrointestinal, weight loss, and neurological.[2] Severe adverse events and withdrawals due to adverse events were not consistently reported for miglustat, but in Type 3 patients, adverse events were severe enough to necessitate prescription of additional therapy in 30% of patients.[2] There was no difference in hemoglobin concentration, liver or spleen volume between miglustat, imiglucerase, or combination treatment for patients with Type 1 Gaucher disease.[2] Platelet count was statistically improved with patients maintained on imiglucerase treatment compared to patients switched to miglustat (20%, p=0.035).[2] For Type 3 patients, there was no apparent difference in hemoglobin concentration, platelet count, and only slight decreases in liver volume or spleen volume after 12 months of treatment with imiglucerase, miglustat or combination therapy (statistical significance not reported).[2] Only 4 patients in miglustat trials experienced bone related outcomes, and there was insufficient evidence to evaluate differences in these outcomes.[2]

A 2011 CADTH report evaluated the efficacy and safety of treatments including eliglustat, miglustat, imiglucerase and velaglucerase for Gaucher Disease.[1] However because this review was published in 2011, the majority of evidence focused on imiglucerase.[1] Overall evidence was of poor quality with substantial evidence from observational studies.[1] Included RCTs were limited by open-label study designs, small sample sizes, short study durations, and poor reporting of randomization and allocation concealment methods.[1] Evidence for imiglucerase primarily reported symptom improvement, and there was only limited data on mortality, quality of life, or long-term skeletal outcomes.[1] One of the included systematic reviews evaluating imiglucerase documented improved bone marrow involvement over 49 months of treatment, but no statistical difference in lumbar spine or femoral bone mineral density Z-scores from baseline.[1] A single, double-blind, non-inferiority RCT (n=34) comparing velaglucerase alfa to imiglucerase, demonstrated comparable hemoglobin levels, liver volume, spleen volume, and platelet counts with both treatments.[1] Three serious adverse events occurred in patients given velaglucerase (seizure, allergic dermatitis, and severe prolonged activated partial thromboplastin time [aPTT]) compared to no events in patients given imiglucerase.[1] Two small trials compared combination treatment with miglustat and imiglucerase compared to imiglucerase alone. Neither trial reported symptom improvement, quality of life, or long-term clinical outcomes, nor was there any difference in hemoglobin level or spleen volume with combination treatment for either study.[1] Evidence was conflicting for platelet count and liver volumes with one trial reporting improvements in liver volume with combination therapy compared to imiglucerase alone (MD 8.5%; p=0.047), but improved platelet count with imiglucerase compared to miglustat (MD 12.6x10^9/L; p=0.035).[1] Overall, authors concluded that there is limited evidence supporting use of ERT with imiglucerase or velaglucerase for Type 1 Gaucher disease, but insufficient data for combination treatment with any agent, and insufficient data for use of substrate reduction therapy.[1]

A third CADTH report evaluating evidence for taliglucerase alfa published in 2015 included 4 studies.[3] Like other drugs, evidence was limited by open-label study designs, lack of comparator groups, small patient populations, lack of intention-to-treat analysis with high attrition rate (29%) in one study, and short study durations (9-12 months).[3] Taliglucerase alfa treatment was evaluated in treatment naïve patients (n=44) and patients with prior imiglucerase use (n=92).[3] In treatment naïve patients, there were statistically significant improvements from baseline in hemoglobin levels (MD 1.4 to 2.2 g/dL), spleen volume (MD -27% to -41%), and liver volume (MD -6.3% to -14.1%).[3] Platelet count was statistically significant from baseline for 60 U/kg (MD 41,494 to 72,600/mm^3) but evidence for 30 U/kg demonstrated inconsistent benefit between studies.[3] In pediatric patients (n=5), the mean change from baseline in height ranged from 4.2 to 7.6% with changes in weight of 9.6 to 14.7% over 9-12 months.[3] There was insufficient evidence to assess quality of life or bone related outcomes, and changes in z-scores, t-scores, and bone mineral density were less than 0.7 for all bone sites indicating little difference over time.[3] No serious adverse events were documented in

treatment naïve patients, but 3-11% of patients switching therapy from imiglucerase had at least one serious adverse event.[3] Of the 4 included studies, 0% (2 studies), 3.4%, and 6.3% of patients withdrew due to adverse events.[3] Overall authors concluded that there was insufficient comparative evidence for taliglucerase alfa and insufficient evidence to evaluate clinically relevant outcomes such as bone crises.[3]

A review of eliglustat for treatment of Type 1 Gaucher disease was published in 2017 from NICE.[4] Eliglustat was recommended within its marketing authorization as an option for treatment of Type 1 Gaucher disease (only when discounts were provided by the manufacturer). This recommendation were primarily based on an analysis of 2 RCTs (comparing eliglustat to placebo or imiglucerase) with supplementary data from a dose comparison study, and a single-arm open-label, phase 2 study.[4] Comparison to imiglucerase was performed in an open-label, non-inferiority trial of patients on ERT with stable disease (n=160).[4] The primary outcome was patients who maintained stable disease for 52 weeks with a non-inferiority margin pre-specified at 25%.[4] Stable disease was defined as patients with changes from baseline which were less than or equal to the following criteria : hemoglobin levels decreased by 1.5 g/dL, platelet counts decreased 25%, spleen volume increased 25%, and liver volume increased 20%.[4] In patients treated with eliglustat, 84.8% (95% CI 76.2 to 91.3) of patients maintained disease stability compared to 93.6% (95% CI 82.5 to 98.7) treated with imiglucerase (difference -8.8%; 95% CI -17.6 to 4.2).[4] There were no clinical difference in bone-related outcomes, hemoglobin, platelet count, organ volumes, symptom improvement scores, or health-related quality of life.[4] Eliglustat was compared to placebo in patients who had not had ERT in the previous 9 months (n=40).[4] Baseline laboratory values for enrolled patients indicated overall mild disease with average hemoglobin level of 12 g/dL, platelet count of 75 to 78 x10^9/L, lumbar spine bone mineral density of -1.1, liver volume 1.3 to 1.4 times normal, and spleen volume 13 to 14 times normal volume.[5] Compared to placebo at 39 weeks, there were statistically significant differences with eliglustat treatment in all laboratory markers including reduction in spleen volume (MD 30%, 95% CI 36.82 to 23.24; p<0.001), liver volume (MD −6.64%, 95% CI −11.37 to −1.91; p=0.0072), hemoglobin level (MD 1.22 g/dL, 95% CI 0.57 to 1.88; p=0.0006), and platelet count (MD 41.06%, 95% CI 23.95 to 58.17; p<0.0001), but no differences in bone disease or symptom improvement scores at 39 weeks.[4] Data from a small (n=26), single-arm, open-label study provided long-term data for up to 4 years, but data was limited by attrition, small sample size, and risk of reporting bias.[4] Safety analysis included 393 patients. Only 3% of patients discontinued treatment due to adverse events, and most common events occurring in at least 10% of patients included headache, joint pain, nasopharyngitis, upper respiratory tract infections, diarrhea, and dizziness.[4] Applicability of this data is limited as few treatment naïve patients were included in the analysis, few patients were poor CYP2D6 metabolizers, and doses of ERT and eliglustat in clinical trials may not reflect doses typically used in practice.[4] In clinical trials, dose of eliglustat was higher than the FDA-approved labeling in approximately 48% of patients.[4]

After review, 4 systematic reviews were excluded due to poor quality (e.g., network meta-analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). [19-22]

Guidelines:
No high-quality guidelines were identified which met quality inclusion criteria.
After review, 3 guidelines were excluded because they did not meet standard quality criteria.[23-25]

Randomized Controlled Trials:
A total of 86 citations were manually reviewed from the initial literature search. After further review, all trials were excluded because of wrong study design (e.g., observational), comparator (e.g., no control), or outcome studied (e.g., non-clinical).

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Appendix 1: Specific Drug Information

Table A1. Clinical Pharmacology and Pharmacokinetics.

Drug Name/Route	Mechanism of Action	Absorption	Metabolism/Excretion	Pharmacokinetics
Eliglustat (Cerdelga®), oral[6]	Inhibitor of glucosylceramide synthase which reduces glucosylceramide accumulation in the tissues	Bioavailability 5%	Metabolized via CYP2D6 and CYP3A4; metabolites excreted in urine (42%) and feces (51%)	Varies based on CYP2D6 metabolizer status; lower numbers represent extensive metabolizers and larger numbers represent poor metabolizers • Half-life: 6.5 to 8.9 hr • Cmax: 12 to 137 ng/mL • AUC: 76 to 1057 ng*hr/mL • Vd: 835 L (extensive)
Imiglucerase (Cerezyme®), intravenous[26]	Analogue of human enzyme B-glucocerebrosidase which catalyzes the hydrolysis of glucocerebrosidase to glucose and ceramide and decreases glucocerebrosidase accumulation.	NA	NA	• Half-life: 3-10 minutes • Cmax: NR • AUC: NR • Vd: 0.09 to 0.15 L/kg
Miglustat (Zavesca®), oral[7]	Competitive and reversible inhibitor of glucosylceramide synthase which reduces glycosphingolipid biosynthesis and the amount of glycosphingolipid build-up in tissues	Bioavailability 97% (decreased 36% when administered with food)	Renal excretion; 67% unchanged in urine	• Half-life: 6-7 hours • Cmax: NR • AUC: NR • Vd: 83-105 liters
Taliglucerase alfa (Elelyso®), intravenous[11]	Recombinant analog of human lysosomal glucocerebrosidase that catalyzes the hydrolysis of glucocerebroside to glucose and ceramide and decreases glucocerebrosidase accumulation.	NA	NA	• Half-life: 29-32 hours • Cmax: NR • AUC: 2984 to 6459 ng*h/mL • Vd: 8.8 to 10.7 L
Velaglucerase alfa (Vpriv®), intravenous[12]	Hydrolytic lysosomal glucocerebroside-specific enzyme which catalyzes the hydrolysis of glucocerebroside, reducing the amount of accumulated glucocerebroside.	NA	NA	• Half-life: 11-12 minutes • Cmax: NR • AUC: NR • Vd: 108 mL/kg

Abbreviations: AUC = area under the curve; Cmax = maximum concentration; CYP = cytochrome P450; kg = kilogram; L = liters; NA = not applicable; ng = nanogram; NR = not reported; Vd = volume of distribution

Table A2. Use in Specific Populations

Population	Eliglustat [6]	Imiglucerase[26]	Miglustat [7]	Taliglucerase alfa[11]	Velaglucerase alfa[12]
Pregnancy	Little human data available (20 pregnancies); No effects on pregnancy were noted in rabbit studies, but fetal abnormalities and maternal toxicity were noted in rat studies	No animal reproduction studies conducted	Little human data available. In rat and rabbit studies, decreased live births, maternal death, and decreased fetal weight were observed.	Little human data available. No evidence of embryo-fetal toxicity in rat or rabbit animal studies	Little human data available. No evidence of embryo-fetal toxicity in rat or rabbit animal studies
Lactation	No human data available; drug and metabolites were present in milk in animal studies	No human or animal data available	No data available. Presence in human milk is unknown.	No data available	Presence in human milk is unknown.
Pediatric	Safety and effectiveness in pediatric patients have not been established	Studied in children 2-16 years of age. Safety and efficacy in patients < 2 years has not been established.	Efficacy and safety have not been established	Only 14 pediatric patients were included in clinical trials. Pediatric patients experienced a higher frequency of vomiting (n=4/9) compared to adults. There is insufficient data to inform dosing in patients < 4 years of age.	Studied in children 4-17 years of age (20 pediatric patients). Safety and effectiveness in patients < 4 years of age has not been established.
Geriatric	Studies did not include patients greater than 65 years of age	NA	Studies did not include patients greater than 65 years of age. Caution is recommended due to greater frequency of hepatic, renal and cardiac comorbidities.	There is insufficient data to determine differences between geriatric and adult patients. Only 8 patients greater than 65 years of age were included in clinical trials.	In clinical studies, 56 patients were 65 years of age or older. No differences were observed based on age.
Renal impairment	Avoid use in patient with extensive CYP2D6 metabolism and end stage renal disease or patients with intermediate or poor metabolism and any degree of renal impairment	NA	Dose reduction recommended in patients with renal impairment	NA	NA
Hepatic impairment	Dose adjustment recommended based on degree of impairment, CYP2D6 metabolism, and concomitant use of CYP2D6 or CYP3A4 inhibitors	NA	NA	NA	NA

Drug Safety:

Boxed Warnings: None

Risk Evaluation Mitigation Strategy Programs: None

Contraindications:

- Imiglucerase, miglustat, taliglucerase alfa, velaglucerase alfa: None
- Eliglustat: Patients with altered CYP2D6 metabolism due to risk of cardiac arrhythmias from prolonged PR, QTc, and QRS intervals.[6]
  - Extensive metabolizers who have:
    - moderate or severe hepatic impairment
    - mild hepatic impairment and take a strong or moderate CYP2D6 inhibitor
  - Extensive or intermediate metabolizers who take a strong or moderate CYP2D6 inhibitor and a strong or moderate CYP3A inhibitor
  - Intermediate and poor metabolizers who have:
    - Any hepatic impairment
    - A strong CYP3A inhibitor

Table A3. Summary of Warnings and Precautions.[6,7,11,12,26]

Warning/Precaution	Eliglustat	Imiglucerase	Miglustat	Taliglucerase alfa	Velaglucerase alfa
Hypersensitivity reactions		X (primarily associated with IgG antibodies)		X	X
Development of IgG antibody		X			
Peripheral neuropathy			X		
Tremor			X		
Diarrhea and Weight Loss			X		
Reductions in Platelet Count			X		
ECG changes and potential for cardiac arrhythmias	X				
Pre-existing cardiac conditions	X				
Combination use with Class IA or Class III antiarrhythmic drugs	X				

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) 1946 to April Week 2 2019

1	exp Gaucher Disease/	4473
2	eliglustat.mp.	53
3	imiglucerase.mp.	344
4	miglustat.mp.	382
5	velaglucerase.mp.	72
6	taliglucerase.mp.	32
7	2 or 3 or 4 or 5 or 6	755
8	1 and 7	438
9	limit 8 to (english language and humans)	385
10	limit 9 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 guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	86

Appendix 3: Key Inclusion Criteria

Population	Patients with Gaucher Disease
Intervention	Any FDA-approved pharmacological treatment
Comparator	Placebo or active comparator
Outcomes	Symptoms, morbidity, mortality, quality of life, functional status
Timing	Any duration
Setting	Outpatient

Gaucher Disease

Goal(s):

- Ensure medically appropriate use of drugs for Gaucher disease

Length of Authorization:

Up to 12 months

Requires PA:

- Drugs for Gaucher disease (pharmacy and physician administered claims)

Covered Alternatives:

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

Table 1. FDA-Approved Minimum Ages

Drug	Age
Eliglustat	18
Imiglucerase	2
Miglustat	18
Taliglucerase alfa	4
Velaglucerase alfa	4

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Is the request for continuation of therapy previously approved by FFS?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4
4. Is the request from a provider experienced in the treatment of Gaucher disease?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
5. Is the request for treatment of Type 1 Gaucher Disease? Note: Type 1 disease is characterized predominately by bone involvement without CNS symptoms. Drugs are not FDA-approved for Type 2 or 3 Gaucher disease, and efficacy in other types of Gaucher disease has not been established.	**Yes**: Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the request for an FDA-approved age in Table 1?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Does the patient have current symptoms characteristic of bone involvement such as: a. Low platelet count b. Low hemoglobin and hematocrit levels c. Radiologic bone disease, T-score less than -2.5 or bone pain d. Delayed growth in children (<10th percentile for age) OR e. Splenomegaly or hepatomegaly?	**Yes:** Go to #8 Document baseline labs and symptoms	**No:** Pass to RPh. Deny; medical appropriateness
8. Is the request for combination treatment with more than one targeted therapy for Gaucher disease?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #9
9. Is the request for enzyme replacement therapy?	**Yes:** Go to #10	**No:** Go to #11
10. Is the request for a non-preferred product and will the prescriber consider a change to a preferred product? Message: Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class. Approve preferred therapy for up to 6 months.	**No:** Approve for up to 6 months

Approval Criteria		
11. Does the patient have a documented contraindication, intolerance, inadequate response, or inability to access or adhere to enzyme replacement therapy?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness
12. Is the request for eliglustat?	**Yes:** Go to #13	**No:** Approve for up to 6 months
13. Does the patient have cardiac disease, long-QT syndrome, or is currently taking a Class IA or Class III antiarrhythmic medication?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #14
14. Does the patient have moderate to severe hepatic impairment?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #15
15. Does testing for CYP2D6 metabolizer status indicate extensive, intermediate or poor CYP2D6 metabolism?	**Yes:** Go to #16	**No:** Pass to RPh. Deny; medical appropriateness
16. Is the dose consistent with FDA labeling based on CYP2D6 metabolism and use of concomitant CYP inhibitors (see FDA labeling for full details)?	**Yes:** Approve for up to 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there documentation based on chart notes that the patient experienced a significant adverse reaction related to treatment for Gaucher disease?	**Yes**: Go to #2	**No:** Go to #3
2. Has the adverse event been reported to the FDA Adverse Event Reporting System?	**Yes:** Go to #3 Document provider attestation	**No:** Pass to RPh. Deny; medical appropriateness
3. Has the patient been adherent to current therapy?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
4. Is there objective documentation of benefit based on improved labs or patient symptoms?	**Yes:** Approve for up to 12 months Document labs and patient symptoms	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 11/19 (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

New Drug Evaluation: amifampridine tablets, oral

Date of Review: November 2019
Generic Name: amifampridine phosphate
amifampridine

End Date of Literature Search: 07/24/2019
Brand Name (Manufacturer): Firdapse® (Catalyst Pharmaceuticals, Inc)
Ruzurgi® (Jacobus Pharmaceutical Company, Inc)
Dossier Received: Firdapse® (yes); Ruzurgi® (no)

Research Questions:

1. What is the efficacy or effectiveness of amifampridine in the treatment of Lambert-Eaton Myasthenic Syndrome (LEMS) compared to placebo or other pharmacotherapy?
2. Is amifampridine safe for the treatment of LEMS?
3. Are there subgroups of patients (i.e. those based on age, gender, ethnicity, disease severity, or comorbidities) that are associated with more effectiveness or harm while treated with amifampridine?

Conclusions:

- In two trials with 64 LEMS patients, there was low quality evidence that amifampridine was associated with a statistically significant least squares mean difference (LSMD) in quantitative myasthenia gravis (QMG) score at 4 days, but not after 14 days of treatment [(LSMD of -6.54; 95% CI -9.78 to -3.29) and (LSMD of -1.7; 95% CI -3.4 to 0), respectively].[1,2] The QMG scale ranges from 0-39, with higher scores indicating greater impairment and clinically meaningful change has been suggested as a decrease in 2.6 points or more.[1,2]
- There was low quality evidence that amifampridine demonstrates a statistically significant improvement in the subject global impression (SGI) score in LEMS patients after treatment versus placebo at 14 days (LSMD of 1.8; 95% CI 0.7 to 3.0) and also at 4 days (LSMD 2.95; 95% CI 1.53 to 4.38).[1,2] It remains unknown if a 2-3 point difference in the SGI score represents a clinically relevant or noticeable to the patient since this outcome has not been validated in other clinical trials.
- There was low quality evidence that a greater percentage of placebo patients experienced decreased mobility at day 4 based on the Triple Timed Up and Go test (3TUG) measurement compared to patients in the continuous amifampridine group (72.2% vs. 0%, respectively; $p<0.0001$).[3]
- There is no data to compare different amifampridine formulations, and it is unclear if the observed changes in QMG score, SGI score, or the 3TUG test correlate to actual changes in disease progression, functional status, or quality of life.
- Amifampridine use is associated with seizure risk and other adverse reactions such as dysesthesia, upper respiratory tract infection, abdominal pain, dyspepsia, nausea, diarrhea, headache, elevated liver enzymes, back pain, muscle spasms, and hypertension.[4]
- There is insufficient evidence to evaluate the safety and efficacy of amifampridine in any subgroups of patients with LEMS.
- There is insufficient evidence to evaluate the long-term safety and efficacy of amifampridine in LEMS treatment beyond 14 days.

Author: Victor Rojo, Pharm.D. Candidate, 2020

Recommendations:

- Create a new PDL class for LEMS agents.
- Implement prior authorization criteria for amifampridine **(Appendix 2).**
- Review costs in executive session.

Background:

Lambert-Eaton myasthenic syndrome (LEMS) is a rare autoimmune neuromuscular disorder characterized by deficient nerve impulse transmission and progressively debilitating muscle weakness.[5] In LEMS patients, it is believed that antibodies to the voltage-gated calcium channels (VGCCs) prevent depolarization of the presynaptic neuron and subsequent release of the neurotransmitter acetylcholine (ACh) which is normally responsible for stimulation of myocyte activity.[6,7] With VGCC blockade, calcium ions are unable to influx the presynaptic cell which results in neuromuscular transmission impairment.[6] The $alpha_1$ subunit of a VGCC provides several binding sites, including the common P/Q-type which are believed to be the primary target for autoantibodies in LEMS.[7]

Patients with LEMS typically present with fatigue and strength deficiency notably in the proximal leg muscles.[5] This weakness impairs mobility and may progress to other muscles of the hands, feet, and eventually the head.[5] As more cranial muscles become affected, there is increased evidence of chewing or swallowing difficulties, speech impairment, ptosis, and visual disruption.[8-11] Other common symptoms of autonomic neuropathy in LEMS include hypohidrosis, xerostomia, and dry eyes.[9,10] Though symmetrical muscle involvement is the predominant presentation in LEMS, unilateral, regional weakness has been documented in patients as well.[11] Approximately half of all LEMS cases are paraneoplastic manifestations and caused by a small cell lung carcinoma (SCLC).[8,12,13] VGCCs are expressed on the surface of SCLC cells and it has been hypothesized that antibodies produced to fight SCLC cells cross-react with VGCCs at the neuromuscular junction.[8,12,13] Treatment of the underlying malignancy has been shown to significantly improve symptoms in patients with concurrent LEMS and SCLC.[8] Patients with LEMS but no evidence of SCLS are categorized as non-paraneoplastic autoimmune LEMS or non-tumor LEMS (NT-LEMS).[8,12,13] In the absence of cancer, NT-LEMS patients do not appear to have a shortened life span, but the disease may impact quality of life.[8] The prevalence of LEMS is estimated to be roughly 3 persons per 1,000,000.[13] Claims data from April 2018 through March 2019 revealed 8 unique patients diagnosed with LEMS in Oregon's Fee-for-Service (FFS) and Coordinated Care Organizations (CCOs).

There is no known cure for LEMS but a variety of agents have been utilized to provide symptomatic treatment. Agents that increase neurotransmitter release at the neuromuscular junction have been shown to assist with LEMS-related muscular dysfunction.[14] Until 2018, guanidine was the only agent FDA-approved for symptomatic relief of muscle weakness and fatigue in patients with LEMS.[14-16] However, guanidine use has been limited due to serious adverse effects including bone marrow depression and renal failure.[14-16] Cholinesterase inhibitors such as pyridostigmine have been used as monotherapy to treat LEMS symptoms with modest success.[15,17] Pyridostigmine used in combination with low doses of guanidine was determined to be effective and safer than guanidine monotherapy, although, pyridostigmine has also demonstrated dose-dependent adverse effects such as nausea, abdominal cramping, and diarrhea.[18] 4-aminopyridine (dalfampridine) had been tested in the past, but its usefulness was limited by the potential to cause seizures and other central nervous system adverse effects.[14,19]

Immune system modulators have also been utilized to treat LEMS symptoms. Intravenous immunoglobulin (IVIG) at variable doses and frequencies may improve limb strength.[20,21] Immunosuppressive treatments such as mycophenolate, cyclosporine, and rituximab have been used, however, delayed response to treatment and significant adverse effects limit their widespread use.[12,14,16,19,22,23] Azathioprine combined with prednisone has demonstrated some symptomatic improvement in LEMS patients, but with a recommended dose taper of prednisone to reduce toxicity.[12,22] In severe or refractory muscle weakness due to LEMS,

immunomodulating therapy has been used with mixed benefit.[12,14 21] Some studies have suggested positive peripheral muscle outcomes in LEMS treatment with plasmapheresis, though a minimum of five exchanges may be necessitated.[24]

Amifampridine (3,4-DAP or 3,4-Diaminopyridine) has been a rational LEMS treatment option for many years.[14,19] Amifampridine is thought to improve ACh release from the presynaptic neuron by blocking potassium channels and prolonging depolarization of the nerve terminal followed by an increase in calcium influx and ACh efflux.[14] Until recently amifampridine never had formal FDA approval, although the drug had been reported to be safe and effective in human studies.[19] Jacobus Pharmaceutical Co, Inc (JPC) had historically made amifampridine available to patients in the United States for free through a compassionate use program.

The goal of LEMS treatment is to provide symptomatic relief and improve quality of life. A variety of assessments have been used in clinical trials to assess LEMS therapy outcomes. The QMG is a 39 point assessment scale in which the physician rates a patient's muscle strength on a scale of 0 (no weakness) to 3 (severe weakness) in 13 different parameters such as ability to swallow, facial muscle function, hand-grip strength, and vital capacity.[1,25] One study defined a minimal clinically important difference (MCID) in QMG to be a change of 2.6 points when used as a primary outcome measure.[25] The subject global impression (SGI) score is a patient-rated scale of 1 (terrible) to 7 (delighted) that reflects the patient's global impression of how they feel symptoms are being managed with treatment.[1,2] No clinically important difference was identified for SGI. Other scales to evaluate patient functional improvement and severity of illness have been reported in the literature such as the Clinical Global Impressions (CGI) scale.[26] The CGI-I is a 7-point scale designed to assess improvement in generalized patient function which ranges from 1 (very much improved) to 7 (very much worse).[26] The CGI-S is also a 7-point scale but is focused on assessment of patient mental health and scored from 1 (normal, not at all ill) to 7 (among the patients who are most ill).[26] There has been no published literature to support a MCID value for a CGI score in LEMS patient assessment. Other outcomes used in studies to assess the clinical benefit of LEMS therapies have included timed walk tests.[27,28] In the Timed Up-and-Go (TUG) test, patients are timed how long it takes to arise from a seated position, walk 3 meters, and then return to a seated position.[29] The TUG test has been used as an assessment of basic functional mobility in movement disorders of the frail elderly with a suggested MCID of 4 seconds[29] Some trials have used modified versions of the TUG test such as the triple timed up-and-go test (3TUG) which has not been validated as a clinical outcome measure in LEMS patients.[3]

Systematic Reviews:

The Cochrane Collaboration performed a systematic review for the medical treatment of LEMS.[30] The review identified 5 randomized, double-blind, placebo-controlled trials of adult patients with LEMS (N=66).[30] None of the included studies contained formulations of agents FDA-approved for use in LEMS. Participants were treated with amifampridine (3,4-Diaminopyridine) for up to 8 days in 4 of the studies and with IVIg for 8 weeks in one study.[30] At the time of the review, amifampridine was frequently used in Europe for symptomatic LEMS treatment but none of the .[30] The primary outcome was change in muscle strength as measured by the (QMG score or limb muscle strength measured by myometry.[30] The studies were rated as low risk of bias in the major domains, however, allocation concealment had an unclear risk of bias in all but one study.[30]

Four of the studies used a muscle strength scale as a primary or secondary outcome measure and reported significant improvement in muscle strength score or myometric limb measurement after treatment.[30] The four amifampridine studies were not able to be combined for meta-analysis because the primary outcomes reported an alternate muscle strength score from the QMG and lack of details in the scoring systems prevented calculation of an equivalent QMG score.[30] However, there was moderate to high quality evidence from two of the small studies that demonstrated the QMG muscle score assessed between 3 and 8 days was likely to decrease (improve) by a mean of -2.44 points (95% CI -3.65 to -1.22) after treatment with amifampridine compared to placebo.[30] The authors of the IVIg study reported IVIg patients had significant improvement in limb strength as measured by myometry compared to placebo, however, no

QMG score or validated muscle strength assessment tool was used to measure treatment effect.[30] Due to the relatively short study durations, small sample size, and differences between primary outcome measures, there was insufficient data to quantify the true treatment effect of amifampridine (3,4-DAP) and IVIg in LEMS patients.

NEW DRUG EVALUATION: Amifampridine phosphate (Firdapse ™); Amifampridine (Ruzurgi ™)

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:
Amifampridine is an orally administered potassium channel blocker indicated for the treatment of LEMS patients. Amifampridine is proposed to act on presynaptic nerve membranes to cause an influx of calcium ions and a corresponding acetylcholine efflux from the presynaptic neuron to improve muscle activity.[27,28] Firdapse™ (amifampridine phosphate) is FDA approved for the treatment of LEMS symptoms in adults and Ruzurgi™ (amifampridine) is approved in patients aged 6 to less than 17.[27,28]

Firdapse™
The safety and efficacy of amifampridine phosphate was studied in two phase 3, double-blind, randomized, placebo-controlled discontinuation studies (LMS-002 and LMS-003).[27] LMS-002 included adult patients (n=38) with a mean age of 52, a confirmed diagnosis of LEMS, and normal swallowing function.[27] Patients without a history of symptomatic LEMS treatment were required to have a baseline QMG score of at least 5 (minimal symptoms).[27] Patients were also required to have at least 80% forced vital capacity (FVC) of predicted respiratory function or at least 60% for amifampridine-naive patients.[27] Full inclusion and exclusion criteria may be found in the evidence table (**Table 3**). Fifty-four patients initially entered a 3-month open-label titration period to allow investigator to optimize therapeutic response to amifampridine.[27] After roughly 30% of subjects withdrew due to adverse events, lack of efficacy, or personal reasons, patients were then allocated to either 7 days of continued amifampridine therapy or gradual taper to placebo followed by a 7-day maintenance period in a double blinded discontinuation phase. Primary outcome assessments were performed at the conclusion of the two-week period.[27] The primary study endpoints were changes in QMG and SGI scores from baseline to day 14.[27] Secondary endpoints were the CGI-I score on day 14 and the change in Timed 25-Foot Walk (T25FW) test speed from baseline.[1] A 20% change in average 3TUG time was evaluated as an exploratory endpoint. Forty of the 54 patients (74%) entered a 2-year optional open-label, safety assessment of amifampridine treatment.[1]

At 14 days, the mean change in QMG score from baseline was 0.4 for amifampridine and 2.2 for placebo (higher scores indicate worse symptoms) with a difference in least squares means of -1.8 (95% CI -3.4 to 0).[1,27] QMG score changes were not statistically significant based on the reported confidence interval. In contrast, there was a statistically significant change from baseline in SGI score for amifampridine-treated patients versus placebo (-0.8 and -2.6, respectively, lower scores indicate worse outcomes) at 14 days with a LSMD of 1.8 (95% CI 0.7 to 3.0).[1,27] The change from baseline in the secondary endpoint of CGI-I was reported to be lower in amifampridine-treated patients versus placebo (3.6 vs 4.7, respectively – higher scores worse) at day 14 with a statistically significant LSMD of -1.1 (95%CI -2.1 to -0.1). The clinical significance of a 1.8-point change in the SGI score or a 1.1-point change on the CGI-I scale is unknown. The LSMD between amifampridine and placebo in the T25FW test was not statistically significant on Day 14.[1,27]

LMS-003 was a 4-day study of 26 adult patients who were already on amifampridine phosphate through an Expanded Access Program (EAP). Participants were titrated to optimal dose and frequency of amifampridine for at least 1 week before 1:1 randomization to amifampridine phosphate or placebo.[2,27] Unlike LMS-002, this trial did not exclude patients with current use of dalfampridine orguanidine.[2,27] Full inclusion and exclusion criteria may be found in **Table 3.** Blinded study medication was given on days 1 through 3.[2,27] On day 4, doses were administered in clinic where assessments were performed 45 minutes after the last treatment dose.[2,27] Upon study completion, patients were eligible to return to the EAP with open-label amifampridine.[2,27] Primary endpoints were change in QMG and SGI scores from baseline to day 4, while the secondary endpoint was the CGI-I score on day 4.[2,27]

At 4 days, the authors reported a statistically significant change from baseline in the QMG score with the amifampridine group compared to placebo (0.0 vs. 6.54; LSMD -6.54 [95% CI, -9.78 to -3.29]).[2,27] There was also a statistically significant difference in SGI scores in the amifampridine group versus placebo (-0.64 vs. -3.9; LSMD 2.95 [95% CI 1.53 to 4.38]).[2,27] For the secondary outcome of CGI-I score change, there was a statistically significant difference in the amifampridine group versus placebo (3.8 vs. 5.5, p=0.002; 95% CI not reported).[2,27] While the author's did report a statistically significant difference in the 3TUG evaluation, the FDA reviewers had concerns that the outcome was not corrected for multiplicity and could represent a chance finding. Therefore, the manufacturer did not include the 3TUG outcome in the labeling and details will not be presented.

Ruzurgi™

A different formulation of amifampridine was approved by the FDA for the treatment of LEMS in patients aged 6 to less than 17 years.[28] Amifampridine safety and efficacy was studied in a double-blind placebo-controlled discontinuation trial, 3,4-DAP Product Efficacy Research (DAPPER). [3,28] Primary efficacy was assessed through percent change in the Triple Timed Up and Go test (3TUG) and the main secondary endpoint was measured via a LEMS Weakness Self-Assessment Scale (W-SAS).[3,28] The 3TUG was a sponsor modified version of the TUG where patients completed 3 continuous TUG test repetitions instead of one and the 3 lap times were averaged.[3] The investigators claimed this variation of the TUG was necessary to accommodate the neuromuscular fatigue that may affect patients with LEM to different degrees.[3] The W-SAS was a sponsor-developed 7-level categorical scale to demonstrate participant-perceived changes in strength with scores that range from -3 ("much, much weaker") to +3 ("much, much stronger").[3,28] The study was small (n=32), with a blinded treatment period of 4 days, and included only patients with a positive response to continuous 3,4-DAP therapy. [3,28] Specific inclusion and exclusion criteria are listed in **Table 3**.

Fifty-two patients underwent a 4-week outpatient screening and admission period to assess initial eligibility.[3,28] Thirty-two of the patients with a sufficient response to the 3TUG test were randomly assigned to either continue the 3,4-DAP active treatment or were allocated to a taper-to-placebo group.[3,28] Over the next 3.5 days, the amifampridine dose was slowly decreased in the taper-to-placebo group until they were without active treatment for a total of 16 hours.[3,28] The 3TUG outcome measure was the proportion of patients with a >30% deterioration in time. W-SAS scores were also assessed at that time.[3,28]

In LEMS patients, a greater percentage of patients in the taper-to-placebo group deteriorated in the 3TUG test compared to patients in the continuous amifampridine group (72.2% vs 0%, respectively; p<0.0001).[3,28] In addition, the investigators reported a statistically significant mean difference in the W-SAS score for the taper-to-placebo group compared to the continuous amifampridine group (-2.4 vs -0.2 respectively; p<0.0001, lower scores worse).[3,28] The clinical significance of a 2.2-point difference in an unvalidated global assessment tool is unclear.

These trials involved a small number of subjects with very short treatment durations. The long run-in period prior to randomization selected only patients with a clear response to amifampridine which, in a discontinuation study design, may have led to an overestimation of treatment benefit. Since the study population had already been stable on doses of amifampridine, which has a short half-life, there was increased risk for unblinding of patients and investigators during the withdrawal period. The majority of assessment tools used in the amifampridine studies were unvalidated. Certain tools such as the SGI and CGI-I were highly

subjective measures of patient symptoms and function with no clear MCID for clinical interpretation. Mean baseline values of the 3TUG test and the complete data for the T25FW were not reported which made it difficult to assess the two most clinically relevant endpoints of patient ambulatory ability.

Clinical Safety:

The most common adverse effects of amifampridine seen in more than 10% of patients are included in **Table 1**.[27,28] No serious adverse effects were reported in the controlled trials.[1-3] The FDA required the manufacturer to add seizures as a warning/precaution on the label based on animal toxicology studies and clinical findings from structurally related compounds, such as 4-aminopyridine.[27,28] The maximum daily dose of Firdapse® is 80 mg and Ruzurgi® is restricted to 100 mg daily as doses of amifampridine above this threshold have been associated with an increase seizure risk.[27,28] Suggested dosing for amifampridine may be found in **Appendix 1**.

Sufficient data for amifampridine risk assessment does not exist in the following subpopulations: pregnancy, lactation, children under 6 years old, and adults aged 65 and older.[27,28] Amifampridine is metabolized by N-acetyltransferase 2, so poor metabolizers or patients with hepatic impairment are at increased risk of drug exposure and are advised to take the lowest recommended starting dose.[27,28] Amifampridine and its inactive metabolite, 3-N-acetyl amifampridine, are both renally eliminated and should be adjusted to the lowest recommended starting dose in patients with renal impairment.[27,28] All subgroups should be monitored closely for intolerability or negative clinical effects.[27,28]

Table 1. Adverse Reactions in >10% of LEMS Patients Newly Treated with Amifampridine*[27,28]

Adverse Reaction	Amifampridine (n=143 combined)
Dysesthesia (paresthesia, dysesthesia, oral dysesthesia)	62-69%
Upper respiratory tract infection	33%
Abdominal pain	14-25%
Dyspepsia	17%
Diarrhea	14%
Headache	14%
Elevated liver enzymes	14%
Nausea	10-14%
Back pain	8-14%
Hypertension	12%
Muscle spasms	6-12%
Dizziness	10-12%

*=placebo rates not available

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Improvement in muscle strength
2) Improvement in ambulation
3) Serious adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoints:

1) Quantitative Myasthenia Gravis (QMG) score
2) Subject Global Impression (SGI)
3) Triple Timed Up and Go test (3TUG)

Table 2. Pharmacology and Pharmacokinetic Properties.[27,28]

Parameter	
Mechanism of Action	Produces calcium influx into, and subsequent acetylcholine release from, presynaptic nerve membrane via potassium channel blockade
Oral Bioavailability	Rapidly absorbed, and peak plasma concentration (C_{max}) were reached 30 to 90 minutes after ingestion in the fasting state; roughly ~41%-52% decrease in C_{max} and ~9%-23% decrease in AUC0-∞, and delay in T_{max} by ~1 hour when amifampridine was administered with high fat meal compared to fasted state (Ruzurgi)
Distribution and Protein Binding	467 L (Firdapse); 357 – 1383 L (Ruzurgi); 25.3% protein binding (Ruzurgi)
Elimination	93-100% (Firdapse); >65% (Ruzurgi); Eliminated as unchanged amifampridine and 3-N-acetyl amifampridine
Half-Life	1.8-2.5 hours (Firdapse), 3.6-4.2 hours (Ruzurgi)
Metabolism	Via N-acetyltransferase to 3-N-acetylamifampridine (inactive metabolite); rate and extent of metabolism of amifampridine is affected by polymorphism in the NAT2

Abbreviations: L = liters; NAT2 = N-acetyltransferase gene 2

Table 3. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Oh et al.[1,27] Phase 3 MC RCT, DB, PC, withdrawal study 91-day open-label run in period followed by 14-day randomized DB treatment	1. Amifampridine phosphate (20-80 mg/day) 2. Taper to Placebo Dosed orally tid-qid x14 days	Demographics: - Mean Age: 52 (range: 21-88) - Female: 61% - White: 90% - PEF ≥100%: 55% - Positive VGCC antibody: 92% - Hx Cancer: 16% - Treatment-experienced: 26% - Baseline QMG, Part 2 Day 1: 6 +/- 4 Key Inclusion Criteria: - Age ≥ 18 - Treatment-naïve QMG score ≥5 - FVC ≥80% predicted for treatment-experienced; ≥60% for treatment-naive - Normal swallowing function - Completion of anti-cancer treatment ≥3 months prior to screening Key Exclusion Criteria: - Known seizure hx - Active brain metastases - Serious electrocardiogram abnormalities - concurrent use of dalfampridine or any form of 3,4-DAP - IVIg or plasmapheresis in previous 90 days, guanidine within previous 7 days, or rituximab within previous year	ITT: 1. 16 2. 22 Attrition: 1. 0 2. 2 (9%)	Primary Endpoints: 1. LSM CFB in QMG Amifampridine: 0.4 Placebo: 2.2 MD: -1.8* (95% CI, -3.4 to 0.0) *= reported -1.7 p = 0.0452 2. LSM CFB in SGI Amifampridine: -0.8 Placebo: -2.6 MD: 1.8 (95% CI, 0.7 to 3.0) p = 0.0028 Secondary Endpoint: LSM CFB CGI-I Amifampridine: 3.6 Placebo: 4.7 MD: -1.1 (95% CI -2.1 to -0.1) p=0.0267 CFB in T25FW in ft/min Amifampridine: -1.16 Placebo: -9.67 MD: -8.51 (95% CI, -26.77 to 43.79) p-value = 0.6274 All outcomes evaluated at Day 14	NA for all	SAEs: 1. 0 2. 0 Discontinuation due to Adverse Events: 1. 0 2. 2 TEAEs During Open Label Run-in: (N = 53) -Oral paresthesia: 21 (39.6%) -Digital paresthesia: 18 (34%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear. Randomization and allocation concealment methods not documented. Performance Bias: Unclear. Subjects reportedly blinded, but methods undefined. Possibility of unblinding due to dose withdrawal study design. Detection Bias: Unclear. Assessors reportedly blinded, but methods undefined; blinding potentially broken due to known adverse effects such as dysesthesia Attrition Bias: Low. <10% overall attrition and between-group dropout rate. Reporting Bias: High. Not all outcome data reported in PP and ITT analyses. Published trial data is inconsistent with FDA analysis. QMG outcome reported to be statistically significantly different in favor of treatment but CI values are contradictory. Other Bias: Unclear. Study was funded by manufacturer. Many major authors served as consultants for or received research funding from manufacturer. **Applicability**: Patient: Adult patients only; mostly white. 3-month run-in period where roughly 30% patients withdrew mostly for adverse effects; extensive exclusion criteria limits applicability notably patients with respiratory or cardiac dysfunction. Intervention: Efficacy evaluation period over 14 days. Study dosing consistent with clinical practice dosing Comparator: Taper to placebo comparator. Study only enrolled subjects known to respond to amifampridine. Guanidine may have been a more appropriate comparator. Outcomes: QMG, SGI, and CGI-I were short-term subjective outcome measures with potential for inconsistent interpretation. T25FW not validated as outcome measure for LEMS patients and subject to variability. Setting: 18 sites within the United States, European Union, and Russian Federation

2. Shieh et al.[2, 27] Phase 3 RCT, DB, PC, withdrawal study	1. Amifampridine phosphate (30-80 mg/day) 2. Taper to Placebo Dosed orally tid-qid x4 days	Demographics: - Mean Age: 54 (range: 31-75) - Female: 62% - White: 81% - Mean BMI: 29.4 (range: 20.6-40.1) kg/m2 - PEF ≥100%: 92% - Positive VGCC antibody: 88% - Cancer: 23% - Daily amifampridine dose at study entry: 61.5 mg ± 18.60 - Baseline QMG: 1. 7.8 +/- 4.2 2. 8.5 +/- 5.4 - Baseline SGI: 1. 6.1 +/- 0.9 2. 5.8 +/- 0.9 Key Inclusion Criteria: - Age ≥18 - Diagnosis of LEMS - Cancer patients required to have completed anticancer treatment ≥3 months before study entry Key Exclusion Criteria: - Clinically significant prolonged interval on ECG within the previous 12 months - Hx of seizure disorder - Active brain metastases - Inability to ambulate - Pregnant or lactating females - Inability to d/c immunomodulatory treatment within 3 weeks before study entry	ITT: 1. 13 2. 13 Attrition: 1. 0 2. 0	Primary Endpoints: 1. CFB in QMG Amifampridine: 0.7 Placebo: 7.1 RR: -6.54 (95% CI, -9.78 to -3.29) p = 0.0004 2. CFB in SGI Amifampridine: -0.3 Placebo: -2.9 RR: 2.95 (95% CI, 1.53 to 4.38) p = 0.0003	NA for all	SAEs: 1. 0 2. 0 TEAEs During Open Label Run-in: (N = 53; FDA included both Oh and Shieh studies) -Paresthesia (included paresthesia, oral paresthesia and oral hypoesthesia) 26 (49%) -URTI 21 (40%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear. Randomization and allocation concealment undefined. Performance Bias: Unclear. Subjects blinded, but blinding methods undefined. Detection Bias: Unclear. Assessors blinded, but blinding methods undefined. Attrition Bias: Low. No missing data. Reporting Bias: High. 3TUG time was pre-specified as an exploratory outcome, but data not reported in the analysis. Many outcomes reported in detail but were not pre-specified in methods (forced vital capacity, head lift 45°). Other Bias: Unclear. Conflicts of interest not reported. Study author has served as consultant for manufacturer. **Applicability**: Patient: Adult patients only; all participants selected from expanded access program Intervention: Study dosing consistent with clinical practice dosing Comparator: Taper to placebo comparator; Study only enrolled subjects known to respond to amifampridine. Guanidine may have been a more appropriate comparator. Outcomes: Efficacy endpoints were subjective; QMG and SGI scores at 4-days with no long term data available Setting: 3 centers in the United States

3.DAPPER [3,28] Phase 2, multicenter, RCT, PC, DB, withdrawal study 4-week screening followed by 1-week assessment	1. Continuous 3,4-DAP 2. Taper to placebo Duration: 7 days tx; 4-week follow-up 3,4-DAP doses: -30 mg/day in 3 divided doses up to 100 mg/day max	Demographics: Median age: -3,4-DAP group: 49 -taper to PBO: 63.5 Female: 66% White: 91% Median age at time of LEMS diagnosis: -3,4-DAP group: 46 -taper to PBO: 59.5 Key Inclusion Criteria: - ≥18 yo; ambulatory - Established LEMS dx - Continuous 3,4-DAP use ≥3 months; ≥3 doses/day of ≥10 mg 3,4-DAP - First morning dose positive response to 3,4-DAP - ≥3 months stable on LEMS-related therapies Key Exclusion Criteria: - Last MAB treatment < 6 months prior - Clinically significant or poorly controlled co-morbidity -Respiratory failure requiring intubation while on 3,4-DAP - Investigational drug use besides 3,4-DAP in last 30 days before study - Pregnant/lactating - Current use of other aminopyridines (e.g., 4-AP) or guanidine - No sufficient baseline response to 3,4-DAP at baseline to detect a ≥30% decline during 3,4-DAP withdrawal	ITT: 1. 14 2. 18 Attrition: 1. 0 2. 0	Primary Endpoint: >30% deterioration in final 3TUG test performance upon withdrawal of 3,4-DAP 1. 0/0% 2. 13/ 72.2% P<0.0001 No CI reported Secondary Endpoint: Subject Self-Assessment of LEMS-Related Weakness (W-SAS) Final Score: "Somewhat weaker", Much weaker" or "Much much weaker": 1. 3 (21%) 2. 17 (94%) P<0.0001	72.2% /2 73%/2	SAEs: 1. 0 2. 1 TEAEs from Expanded Access Dataset, N = 159) -paresthesia 56 (36.5%) -fall 21 (13.2%) -diarrhea 20 (12.6%) -pneumonia 16 (10.1%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear. Participants randomized centrally 1:1 but randomization and allocation concealment methods undefined; Sponsor determined if individual eligibility was met based on 3TUG pre-trial assessment Performance Bias: Unclear. Identical tablets and centralized packaging used to ensure blinding of all subjects and investigators; only responders to active agent were enrolled and randomized Detection Bias: Unclear. Central reader blinded to treatment videotaped and scored the 3TUG tests. FDA noted several data discrepancies which required re-analysis. Attrition Bias: Low. All patients completed study. ITT population included all patients randomized, as well as patients who were replaced due to withdrawal of consent after randomization but prior to admission. Reporting Bias: Unclear. Baseline 3TUG scores unavailable for comparison. Other Bias: Unclear.; Jacobus Pharmaceutical Company, Inc, sponsored the research; lead authors were consultants for manufacturer **Applicability**: Patient: All patients studied were adults so efficacy in children is unclear. FDA approval was based on efficacy and safety data from expanded access programs. Intervention: Mean TDD at baseline was roughly 75 mg. Unable to evaluate dose response with respect to clinical efficacy especially in pediatric population based on this study Comparator: Taper to placebo. Guanidine may have been a more appropriate comparator for adult population. Outcomes: 3TUG performance after only 1-week, long term effects are unclear Setting: 7 centers across the United States

Abbreviations [alphabetical order]: 3TUG = triple timed up and go.; ARR = absolute risk reduction; BMI = body mass index; CFB = change from baseline; CGI-I: Clinical Global Impression-Improvement Score; CI = confidence interval; DB = double blind; ECG = electrocardiogram; FVC = forced vital capacity; Hx = history; ITT = intention to treat; LEMS = Lambert-Eaton Myasthenic Syndrome; LSM = least squares mean; MAB = monoclonal antibody; MC = multicenter; MD = mean difference; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = not significant; PBO = placebo; PC = placebo controlled; PEF = post-exercise facilitation; PP = per protocol; QID = four times daily; QMG = quantitative myasthenia gravis score; RCT = randomized

controlled trial; SAE = serious adverse event; SGI = subject global impression; T25FW = timed 25-foot walk test; TDD = total daily dose; TID = three times daily; URTI = upper respiratory tract infection; VGCC = voltage-gated calcium channel.

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Appendix 1: Prescribing Information Highlights

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

RUZURGI (amifampridine) tablets, for oral use
Initial U.S. Approval: 2018

INDICATIONS AND USAGE

RUZURGI is a potassiumchannel blocker indicated for the treatment of Lambert-Eaton myasthenic syndrome (LEMS) in patients 6 to less than 17 years of age. (1)

DOSAGE AND ADMINISTRATION

- Patients 6 to less than 17 years of age weighing 45 kg or more:
  - Initial dosage is 15 mg to 30 mg daily, in divided doses
  - Increase daily in 5 mg to 10 mg increments, divided in up to 5 doses daily
  - Maximum single dose is 30 mg; maximum daily dosage is 100 mg (2.1)
- Patients 6 to less than 17 years of age weighing less than 45 kg:
  - Initial dosage is 7.5 mg to 15 mg daily, in divided doses
  - Increase daily in 2.5 mg to 5 mg increments, divided in up to 5 doses daily
  - Maximum single dose is 15 mg; maximum daily dosage is 50 mg (2.1)
- When patients require a dosage in less than 5 mg increments, have difficulty swallowing, or require feeding tubes, a 1 mg/mL suspension can be prepared. (2.2)
- For patients with renal or hepatic impairment or who are known N-acetyltransferase 2 poor metabolizers, use the lowest recommended initial dosage. (2.3, 2.4, 2.5)

DOSAGE FORMS AND STRENGTHS

Tablets: 10 mg, functionally scored (3)

CONTRAINDICATIONS

- History of seizures (4)
- Hypersensitivity to amifampridine or other aminopyridine (4)

WARNINGS AND PRECAUTIONS

- RUZURGI can cause seizures. Consider discontinuation or dose-reduction of RUZURGI in patients who have a seizure while on treatment. (5.1)
- Hypersensitivity reactions: If a hypersensitivity reaction such as anaphylaxis occurs, RUZURGI should be discontinued and appropriate therapy initiated. (5.2)

ADVERSE REACTIONS

The most common adverse reactions (incidence at least 10% and at least 2% greater than placebo) are paresthesia/dysesthesia, abdominal pain, dyspepsia, dizziness, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Jacobus at 609-921-7447 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

DRUG INTERACTIONS

- Drugs that lower seizure threshold: The concomitant use of RUZURGI and drugs that lower seizure threshold may lead to an increased risk of seizures. (7.1)
- Drugs with cholinergic effects: The concomitant use of RUZURGI and drugs with cholinergic effects (e.g., direct or indirect cholinesterase inhibitors) may increase the cholinergic effects of RUZURGI and of those drugs, and increase the risk of adverse reactions. (7.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 5/2019

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

FIRDAPSE® (amifampridine) tablets, for oral use
Initial U.S. Approval: 2018

----------INDICATIONS AND USAGE----------
FIRDAPSE is a potassiumchannel blocker indicated for the treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults. (1)

----------DOSAGE AND ADMINISTRATION----------
- The recommended starting dosage is 15 mg to 30 mg daily taken orally in divided doses (3 to 4 times daily). (2.1)
  - Starting dosage is 15 mg daily for patients with renal impairment, hepatic impairment, and in known N-acetyltransferase 2 (NAT2) poor metabolizers (2.2, 2.3, 2.4)
- Dosage can be increased by 5 mg daily every 3 to 4 days. (2.1)
- Dosage is not to exceed a maximum of 80 mg daily. (2.1)
- The maximum single dose is 20 mg. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
- Tablets: 10 mg, functionally scored. (3)

----------CONTRAINDICATIONS----------
FIRDAPSE is contraindicated in patients with:
- A history of seizures (4)
- Hypersensitivity to amifampridine or another aminopyridine (4)

----------WARNINGS AND PRECAUTIONS----------
- Seizures: FIRDAPSE can cause seizures. Consider discontinuation or dose-reduction of FIRDAPSE in patients who have a seizure while on treatment. (5.1)
- Hypersensitivity reactions: If a hypersensitivity reaction such as anaphylaxis occurs, FIRDAPSE should be discontinued and appropriate therapy initiated. (5.2)

----------ADVERSE REACTIONS----------
The most common (> 10%) adverse reactions are: paresthesia, upper respiratory tract infection, abdominal pain, nausea, diarrhea, headache, elevated liver enzymes, back pain, hypertension, and muscle spasms. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Catalyst Pharmaceuticals at 1-844-347-3277 (1-844-FIRDAPSE) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Drugs that lower seizure threshold: The concomitant use of FIRDAPSE and drugs that lower seizure threshold may lead to an increased risk of seizures. (7.1)
- Drugs with cholinergic effects: The concomitant use of FIRDAPSE and drugs with cholinergic effects (e.g., direct or indirect cholinesterase inhibitors) may increase the cholinergic effects of FIRDAPSE and of those drugs, and increase the risk of adverse reactions. (7.2)

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Amifampridine

Goal(s):
- Promote safe and effective use of amifampridine in the treatment of LEMS symptoms

Length of Authorization:
- Initial: 14 days
- Renewal: 1 to 3 months

Requires PA:
- Amifampridine

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 Recommended Dose

Formulation	Minimum age (years)	Weight (kg)	Single Dose Maximum	Cumulative Daily Maximum
Ruzurgi®	≥ 6	≤ 45	15 mg	50 mg
		≥ 45	30 mg	100 mg
Firdapse®	≥ 18		20 mg	80 mg

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is the diagnosis for Lambert-Eaton Myasthenic Syndrome (LEMS)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
4. Is the request for a non-preferred product and will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics Committee.	**Yes:** Inform prescriber of preferred alternatives.	**No:** Go to # 5
5. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is there evidence based on chart notes or claims that the patient has a seizure disorder diagnosis or history of seizures?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #7
7. Is there evidence based on chart notes or claims that the patient has active brain metastases?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #8
8. Does the patient have a documented baseline ECG in the past 12 months demonstrating a QT interval < 450 milliseconds?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Is the amifampridine dose within the appropriate limits? (See **Table 1** in criteria)	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness
10. Has the patient been assessed with a baseline qualitative myasthenia gravis (QMG) exam (score>5), 3TUG walking test, or other validated measure of LEMS patient physical functioning?	**Yes:** Go to #11 Document baseline results.	**No:** Pass to RPh. Deny; medical appropriateness
11. Does the patient have follow-up appointments scheduled during weeks 1 and 2 after the proposed therapy initiation date?	**Yes:** Go to #12 Document appointment dates.	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
12. Will the patient and provider comply with all case management interventions and adherence monitoring requirements required by the Oregon Health Authority?	**Yes:** Approve for 2 weeks	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has the patient been taking amifampridine for ≥1 week AND has there been documented improvement from baseline in ambulation or physical functioning as assessed via the 3TUG, QMG score, or other validated LEMS assessment scale?	**Yes:** Document follow-up assessment scores Go to #2	**No:** Pass to RPh. Deny; medical appropriateness
2. Is the amifampridine dose within appropriate limits? (See **Table 1** in criteria)	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Has the patient experienced any new adverse effects since starting amifampridine therapy (e.g. seizures, arrhythmias)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #4
4. Does the patient have documented evidence of >90% adherence to amifampridine for the previous approval period?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Has the patient been on >30 days of continuous amifampridine therapy?	**Yes:** Approve for 3 months	**No:** Approve for 30 days; Renewal consideration will require documentation of tolerance, clinical benefit, and adherence.

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: Cholbam (cholic acid) capsule, oral

Date of Review: November 2019
Generic Name: cholic acid

End Date of Literature Search: 06/18/2019
Brand Name (Manufacturer): Cholbam™ (Retrophin, Inc.)
Dossier Received: yes

Research Questions:

1. What is the efficacy of cholic acid for treatment of bile acid synthesis disorders (BASDs) due to single enzyme defects (SEDs) or as an adjunctive treatment for peroxisomal disorders (PDs) such as Zellweger syndrome (ZS) pertaining to important outcomes such as hepatic impairment or mortality?
2. Is cholic acid safe for treatment of bile acid synthesis disorders due to SEDs or as an adjunctive treatment for PDs?
3. Are there any subgroups (i.e. age, gender, ethnicity, concomitant diabetes, disease duration or severity) that would particularly benefit or be harmed from treatment with cholic acid?

Conclusions:

- The Food and Drug Administration (FDA) approval of cholic acid was based on a phase 3, nonrandomized, open-label, single-arm compassionate use trial in 85 patients conducted over an 18-year period.[1] There is insufficient evidence from this poor quality trial to demonstrate cholic acid is effective in reducing atypical urinary bile acids patients with BASDs due to SEDs or PD.[2] Accumulation of these hepatotoxic bile acids results in hepatic impairment and injury. Among patients with SED, the percentage of patients with normalized urinary bile acid excretion increased from 2.3% at baseline to 65.1% post-treatment with cholic acid ($P<0.0001$.[2] Among patients with PDs, the percentage with normalized urinary bile acid excretion increased from 33.3% to 85.2% with cholic acid treatment ($P<0.0001$).[2]
- There were only small numbers of adverse effects reported from the manufacturer's phase 1 and phase 3 trials of cholic acid. Diarrhea was the most frequent common adverse effect (2%) in patients with either BASD or Zellweger syndrome, the most common PD.[3] Other adverse events including abdominal pain, neuropathy, esophagitis, nausea, jaundice, and skin lesions, occurred at rates of 1%.[3]
- An extension trial in 15 patients with BASDs with SED was conducted over 10 years in patients that participated in the initial efficacy trial for cholic acid.[4] All patients were alive with their native liver and normal findings on physical examination upon last follow-up.[4] Also, all patients had normal serum liver biochemistry tests, the excretion of atypical bile acid metabolites remained low or in trace amounts, and no patients reported serious adverse effects.[4] Due to the small sample size of this trial, there is insufficient evidence regarding the impact of cholic acid treatment in reducing mortality or hepatic injury in patients with BASDs or PDs.
- The safety and effectiveness of cholic acid on extrahepatic manifestations of bile acid synthesis disorders due to SEDs or PDs including Zellweger spectrum disorders have not been established.[3]

Author: Deanna Moretz, PharmD, BCPS

Recommendations:

- Designate cholic acid as a non-preferred agent on the Preferred Drug List (PDL) of the Oregon Practitioner-Managed Prescription Drug Plan (PMPDP).
- Implement PA criteria for cholic acid to ensure use according to FDA-approved indications (**Appendix 2**).
- Review costs in executive session.

Background:

Biosynthesis of bile acids from cholesterol involves several complex steps catalyzed by at least 15 hepatic enzymes.[5] In bile acid synthesis, cholesterol is altered by a cascade of reactions that add hydroxyl groups, reduce and shorten the side-chain, and conjugate the terminal acid group with glycine or taurine, resulting in the two primary bile acids, chenodeoxycholic acid and cholic acid.[5] Bile acids promote the flow and excretion of bile, assist in the intestinal absorption of fat and fat-soluble vitamins, and provide feedback inhibition of bile acid synthesis. Nine inborn errors of bile acid metabolism have been identified that lead to enzyme deficiencies and impaired bile acid synthesis in humans.[1] Patients with inborn errors of bile acid metabolism cannot synthesize primary bile acids, resulting in reduced bile flow, decreased absorption of fat and fat-soluble vitamins, and accumulation of toxic intermediary cholesterol metabolites.[6] Inborn errors of bile acid metabolism are rare causes of neonatal cholestasis and liver disease in older children and adults.[7] The incidence and prevalence of BASDs are unknown.[8] These disorders have been estimated to account for as many as 1-2% of all childhood cholestatic disorders.[8] However, many cases go undiagnosed or misdiagnosed making it difficult to determine their true frequency in the general population.[8]

Disorders of bile acid synthesis are classified as primary or secondary. Primary BASDs are caused by enzyme defects which result in insufficient production of the 2 primary bile acids and cause overproduction of hepatotoxic bile acids. BASDs are a heterogeneous group of disorders, each of which is associated with a defect of a specific enzyme that is needed in the synthesis of bile acids.[9] Bile acid disorders involving specific enzymes include:

- 3-beta-hydroxy-delta-5-C27-steroid oxidoreductase (3-beta-HSD) deficiency*
- alpha-methylacyl-CoA racemase (AMACR) deficiency
- amino acid n-acyltransferase deficiency
- bile acid CoA ligase deficiency
- cholesterol 7alpha-hydroxylase deficiency
- delta4-3-oxosteroid 5-beta-reductase (AKR1D1 mutation) deficiency*
- oxysterol 7-alpha-hydroxylase deficiency
- sterol 27-hydroxylase deficiency (cerebrotendinous xanthomatosis)
- trihydroxycholestanoic acid CoA oxidase deficiency

  **occurs more frequently than other BASDs[9]*

Secondary BASDs due to peroxisomal disorders are associated with the production of abnormal bile acids and progressive liver disease.[5] Reactions modifying and shortening the cholesterol side-chain take place in mitochondria and peroxisomes.[5] Peroxisomes are small structures within the cytoplasm of cells that catalyze catabolic and anabolic functions critical to cellular metabolism.[10] The defect in patients with PD involves failure to adequately perform the side-chain oxidation of bile acid precursors, which results in accumulation of long-chain bile acids.[5] Zellweger syndrome (ZS) is the most common PD and is generally diagnosed in infancy. During the first year of life, children with ZS will present with multi-organ dysfunction, craniofacial dysmorphism, and significant neurologic deficits.[1] Treatment of ZS includes fat-soluble vitamin supplementation, anti-epileptic drugs to treat seizures, and adrenal replacement therapy if warranted. Cholic acid replacement therapy has only been shown to help relieve signs and symptoms of hepatic disease in patients with ZS.

Diagnosis of inborn errors of metabolism should be considered in infants with conjugated hyperbilirubinemia with low serum gamma glutamyl transpeptidase (GGT) and low or normal serum bile acids measured by conventional testing methods.[7] The atypical bile acid metabolites are generally not detected by the routine or classic methods for bile acid measurement, and mass spectrometric (MS) techniques provide the most appropriate means of characterizing defects in bile acid synthesis.[7] Detection of atypical bile acids in urine and serum can be obtained using fast atom bombardment (FAB-MS), liquid secondary ionization (LSI-MS), or gas chromatography (GC-MS).[5]

The phenotype of bile acid synthetic defects is highly variable.[11] Patients present with varying degrees of hyperbilirubinemia, elevations in serum transaminases and on clinical examination, hepatosplenomegaly.[11] The mortality rate is about 50% in reported cases of SED, many of whom were diagnosed late in the course of liver disease.[12] Those who are diagnosed early may benefit from cholic acid replacement therapy. For those who have significant liver disease, liver transplantation may be the only option. Treatment of PD patients is primarily supportive care.[12]

In the past year, there have been 114 Oregon Health Plan (OHP) patients that have presented with a diagnosis of peroxisomal disorder or a disorder of bile acid and cholesterol metabolism. These disorders are funded by the Health Evidence Review Commission (HERC) on line 60 of the Prioritized List of Health Services.[13] Fourteen patients with these diagnoses are currently enrolled in Fee-For-Service (FFS) and 84 are currently enrolled in a Coordinated Care Organization (CCO), and 16 are no longer eligible for coverage. Of the 114 patients, 4 of them had a pharmacy claim for cholic acid; 3 of them were enrolled in a CCO and 1 patient is a FFS member.

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:
Cholic acid (Cholbam™), an oral bile acid, received FDA approval in 2015 for the treatment of BASDs due to SEDs.[3] Cholic acid is also indicated as an adjunctive treatment for patients with PD, including Zellweger spectrum disorders, who exhibit manifestations of liver disease, steatorrhea, or complications from decreased fat-soluble vitamin absorption.[3] The recommended dosage is 10 to 15 mg/kg once daily or in two divided doses, in pediatric patients and adults.[3]

Cholic acid was approved under the FDA accelerated approval regulations, requiring further adequate and controlled clinical trials to verify the clinical benefit.[9] The FDA approval of cholic acid was based on a phase 3, nonrandomized, open-label, single-arm compassionate use trial in 85 patients (64% with SED and 36% with PD) over an 18-year period.[1] The primary efficacy variables were changes from baseline to post-treatment (mean duration of treatment was 145 weeks) in atypical urinary bile acids, liver chemistries (serum aspartate aminotransferase [AST] and alanine aminotransferase [ALT]), and height and weight percentiles.[2] Additional efficacy variables included changes in serum bilirubin and liver histology.[2]

Enrollment in the trial was based on abnormal urinary bile acid levels by FAB-MS analysis.[2] Using a scoring system based on signal/noise ratio for the major ions, the FAB-MS at baseline and post-treatment were assessed as normal (score 0) or as showing slight (score 1), significant (score 2), or marked (score 3) increases in the levels of atypical bile acids.[2] This semi-quantitative assessment was validated for 3-beta-HSD deficiency and shown to correlate well with quantitative excretion as measured by a targeted tandem MS method.[2] Laboratory assessment of serum AST, serum ALT, and serum bilirubin (total and direct) were performed at baseline and at regular intervals during treatment.[2] A value of 50 IU/L was selected as the upper limit of normal (ULN) for AST and ALT.[2] Percutaneous liver biopsies were performed at baseline (if no historical sample was available) and between 1 and 10 months after treatment initiation.[2] In

patients with ZS, a liver biopsy was performed if there was no contraindication to biopsy that increased the risk of the procedure.[2] Liver biopsies were not required for patients enrolled in the trial. Disease progression was defined as increase of serum bile acids, transaminases, and bilirubin; or cholestasis on liver biopsy.[9]

In the original study protocol, a combination of ursodeoxycholic acid (UDCA) and cholic acid was stipulated as study medication.[2] However, after analysis of urinary bile acids suggested that UDCA could interfere with the intestinal absorption of cholic acid, UDCA was removed as study medication and patients were administered cholic acid as monotherapy.[2] Forty patients received 15 mg/kg cholic acid once daily, and 39 patients had cholic acid in combination with UDCA.[9]

The analysis of the primary outcome was evaluated using a worst-to-best analysis (comparing the least favorable outcome before intervention with the best favorable outcome after intervention) of changes in urinary bile acids.[2] Among patients with SED, the percentage with normal FAB-MS scores (indicating normalized urinary bile acid excretion) increased from 2.3% at baseline to 65.1% post-treatment; the percentage with marked abnormalities decreased from 72.1% to 14.0% post-treatment (P<0.0001).[2] Among patients with ZS, the percentage with normal FAB-MS scores increased from 33.3% to 85.2% with cholic acid treatment (P<0.0001).[2]

For patients with SED and PD, there was a marked increase in the number of patients with normal serum ALT and AST values over the mean treatment period of 145 weeks.[2] In the SED population, only 18.4% had a baseline AST < 50 IU/L, but post-treatment AST values were normal in 85% of the SED population (change: 66.6%, P<0.0001).[2] In the PD population, 7.4% had a baseline AST < 50 IU/L, and post-treatment AST values were normal in 15.4% of the PD population (improvement for 8% of patients, P=0.0073).[2] Treatment with cholic acid improved weight percentiles in patients with SED and those with PD (**Table 3**). The changes in weight percentiles were statistically and clinically significant (P=0.006 and P=0.014) for patients with SED and PD, respectively.[2] Pre- and post-treatment liver biopsies were available for analysis in 4 patients. With the exception of bridging fibrosis and unspecified fibrosis, all histopathologic features were less prominent in post-treatment biopsies than in pretreatment biopsies.[2] Refer to **Table 3** for more details about this study.

The major limitations of the study include: nonrandomized, single arm trial design, many protocol deviations which were identified by the clinical inspection team, and the responder analyses which contained 3 biomarker components (bile acids, transaminases).[9] Documentation of adherence to treatment, concomitant medications, and response to treatment were incomplete during this trial.[9] The choice of a worst-to-best analysis is considered not an acceptable statistical method in biomedical studies due to the risk of a Type 1 error occurring (i.e. detecting an effect that was not present).[14] In addition, the study population was small, narratives of patients who died during the study were incomplete, and clinical laboratory data were missing for some patients.[9] Some subjects had exposure to multiple types of primary bile acids with different dosing regimens.[9] Finally, rates of lost-to-follow-up were high (11/50, 22% of SED patients and 6/29, 21%).[9]

An extension trial in 15 patients with 2 specific bile acid deficiencies (3-beta-HSD (n=13) and AKR1D1 (n=2) mutations) was conducted over 10 years in patients that participated in the initial efficacy trial for cholic acid.[4] The 2 mutations included in this trial have been identified as the most frequent inborn errors of bile acid metabolism.[4] The follow-up evaluations were performed every year and included: 1) physical examination at least once a year; 2) blood liver biochemistry tests including alpha-fetoprotein and total serum bile acids; 3) abdominal ultrasonography; 4) urine bile acid analyses by gas chromatography/mass spectrometry (GC-MS).[4] Bile acid analyses in urine samples were performed and predominant specific atypical bile acids were determined in urine and expressed as a percentage of total urinary bile acids.[4] Liver biopsy specimens were analyzed by the same pathologist and compared to previous biopsies.[4]

The median age at last follow-up and the median time of follow-up with treatment were 24.3 years (range: 15.3–37.2) and 21.4 years (range: 14.6–24.1), respectively.[4] All patients were alive with their native liver, with normal findings on physical examination upon last follow-up visit.[4] Also, all patients had normal serum liver biochemistry tests and the excretion of the atypical metabolites of bile acids remained low or traces in amount, signing a good metabolic control of the primary bile acid synthesis defects.[4] Most patients had normal liver ultrasonography and 4 patients had minor ultrasonographic liver abnormalities.[4] In all patients, serum alpha-fetoprotein (AFP) level was persistently normal and none of the patients developed hepatocellular carcinoma. Alpha-fetoprotein is a glycoprotein that is produced by a variety of tumors including hepatocellular carcinoma and hepatoblastoma. Most studies report elevated AFP concentrations in approximately 70% of patients with hepatocellular carcinoma.

Clinical Safety:

There were only small numbers of adverse effects reported from the 18-year study of cholic acid. Diarrhea was the most frequent common adverse effect (2%) in both the BASD and ZS populations.[9] A summary of common adverse events observed during case reports and clinical trials is presented in **Table 1.**[4] In the extension trial no serious adverse events were observed over 10 years and five women treated at therapeutic doses had given birth to 10 healthy newborns.[4]

Table 1: Common adverse reactions with cholic acid observed in clinical trials[3]

Adverse Reactions	Overall Incidence (n=140)
Diarrhea	3 (2%)
Reflux Esophagitis	1 (1%)
Malaise	1 (1%)
Jaundice	1 (1%)
Skin Lesion	1 (1%)
Nausea	1 (1%)
Abdominal Pain	1 (1%)
Intestinal Polyp	1 (1%)
Urinary Tract Infection	1 (1%)
Peripheral Neuropathy	1 (1%)

The manufacturer recommends discontinuation of cholic acid if liver function does not improve within 3 months of starting treatment, if complete biliary obstruction develops, or if there are persistent clinical or laboratory indicators of worsening liver function or cholestasis.[3] Continued monitoring of liver function is recommended and patients may consider restarting a lower dose when parameters return to baseline.[3]

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

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Mortality
2) Hepatic Impairment
3) Serious adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Disease progression was defined as increase of serum bile acids, transaminases, and bilirubin; or cholestasis on liver biopsy

Table 2. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Bile acid replacement therapy
Oral Bioavailability	Extensively absorbed by passive diffusion along the length of the gastrointestinal tract
Distribution and Protein Binding	N/A
Elimination	Bile as conjugated cholic acid Fecal as unabsorbed cholic acid
Half-Life	N/A
Metabolism	Liver: primary via conjugation

Abbreviations: NA=Not Available

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. Heubi et al.[2] CAC-91-10-10 Phase 3, OL, single arm trial	1. Cholic acid 10 to 15mg/kg po once or divided twice daily Conducted over 18 years. Average duration of treatment was 145 weeks (approximately 12 years).	Demographics: 1. Mean age at diagnosis: 2 yrs 2. Mean age at start of treatment: 3 yrs 3. Gender: Male 59% 4. Disorder type: SED 64% PD 36% Key Inclusion Criteria: A. SED Population: 1. Cholestasis at baseline must meet ≥ 2 of abnormal biomarkers: -ALT/AST > 50 U/L -Total bilirubin > 1 mg/dL, or direct bilirubin > 0.3 mg/dL -Evidence of cholestasis on liver biopsy	ITT: N=85 SED: 54 PD: 31 mITT: (received at least one dose of cholic acid) n=79 SED: 50 PD: 29 Attrition: 1. SED: 7 (13%) 2. PD: 14 (45%)	Primary Endpoint: Percentage of patients with change in normal bile acid metabolites from baseline to post-treatment assessed by urine FAB-MS. a. SED Population: Baseline: 2.3% Post-treatment: 65.1% Change: 62.8% b. PD Population Baseline: 33.3% Post-treatment: 85.2% Change: 51.9% P< 0.0001 for both populations Secondary Endpoint: 1. Percentage of patients with improved liver chemistry from baseline to post-treatment. A. Baseline AST < 50 IU/L SED Population Baseline: 18.4% Post-treatment: 85%	NA NA NA	AE: n=38 (48%) SAE: n=16 (20%) AE leading to drug discontinuation: n=4 (5%) Death n=21 (27%) p-value and 95% CI NR for all	NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: High. Nonrandomized, open label trial design Performance Bias: High. This was an open-label, single-arm study. Detection Bias: High. This study was not blinded. Attrition Bias: High. High drop out in the PD population due to death. Reporting Bias: High. Numerous protocol violations. Use of worst-to-best analysis (comparing the least favorable outcome before intervention with the best favorable outcome after intervention) may overestimate treatment outcomes. Other Bias: Unclear. Sponsored by Retrophin, manufacturer of cholic acid **Applicability**: Patient: Applies to patients with BASDs due to SEDs and PD. Intervention: Cholic acid administered concurrently with another bile acid (ursodeoxycholic acid) in 46% of the patients. Comparator: No comparator used due to ethics of not treating patients with BASDs.

		-Urinary FAB-MS score > 2 B. PD Population: 1. Neurologic evaluation 2. Serum long-chain fatty acids positive 3. Urinary FAB-MS analysis positive for atypical bile acids <u>Key Exclusion Criteria</u>: None were defined for this trial		Change: 66.6% P<0.0001 PD Population Baseline: 7.4% Post-treatment: 15.4% Change: 8% P=0.0073 B. Baseline ALT < 50 IU/L SED Population Baseline: 22.5% Post-treatment: 87.5% Change: 65% P<0.0001 PD Population Baseline: 18.5% Post-treatment: 51.9% Change: 33.4% P=0.0003 2. Change in weight from baseline to post-treatment (absolute percentile rank) SED Population Baseline: 31.1% Post-treatment: 54.9% Change: 23.8% P = 0.006 PD Population Baseline: 8.3% Post-treatment: 25.6% Change: 17.3% P = 0.014	NA NA NA NA NA			<u>Outcomes</u>: Biomarkers used to assess efficacy. <u>Setting</u>: Primarily one site in the United States (Cincinnati Children's Hospital) and additional sites on Canada

<u>Abbreviations</u>: ALT= alanine transaminase; AST=aspartate transaminase; ARR = absolute risk reduction; BASD = bile acid synthesis disorder; CI = confidence interval; FAB-MS= Fast Atom Bombardment ionization–Mass Spectrometry; ITT = intention to treat; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR =not reported; OL = open-label; PD=peroxisomal disorder; PO = oral; PP = per protocol; SED=single enzyme defect; yrs = years

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Appendix 1: Prescribing Information Highlights

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

CHOLBAM (cholic acid) capsules, for oral use
Initial U.S. Approval: 2015

----------INDICATIONS AND USAGE----------
CHOLBAM is a bile acid indicated for:

- Treatment of bile acid synthesis disorders due to single enzyme defects (SEDs). (1.1)
- Adjunctive treatment of peroxisomal disorders (PDs) including Zellweger spectrum disorders in patients who exhibit manifestations of liver disease, steatorrhea or complications from decreased fat soluble vitamin absorption (1.2)

Limitation of use:
The safety and effectiveness of CHOLBAM on extrahepatic manifestations of bile acid synthesis disorders due to SEDs or PDs including Zellweger spectrum disorders have not been established. (1.3).

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

- The recommended dosage is 10 to 15 mg/kg once daily or in two divided doses, in pediatric patients and adults. See prescribing information for weight-based dosing tables. (2.1)
- The recommended dosage in patients with concomitant familial hypertriglyceridemia is 11 to 17 mg/kg once daily or in two divided doses and is adjusted based on clinical response (2.1)
- Monitor AST, ALT, GGT, alkaline phosphatase, bilirubin and INR every month for the first 3 months, every 3 months for the next 9 months, every 6 months during the next three years and annually thereafter. Administer the lowest dose that effectively maintains liver function (2.2)
- Discontinue CHOLBAM if liver function does not improve within 3 months of starting treatment, if complete biliary obstruction develops, or if there are persistent clinical or laboratory indicators of worsening liver function or cholestasis; continue to monitor liver function and consider restarting a lower dose when parameters return to baseline. (2.2, 5.1, 8.6)

Administration Instructions:

- Take with food. (2.3)
- Do not crush or chew the capsules. For patients unable to swallow the capsules, the capsules can be opened and the contents mixed with drink/food (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
Capsules: 50 mg, 250 mg (3)

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

----------WARNINGS AND PRECAUTIONS----------
Exacerbation of Liver Impairment: Monitor liver function and discontinue CHOLBAM if liver function worsens while on treatment (5.1)

----------ADVERSE REACTIONS----------
Most common adverse reactions (≥1%) are diarrhea, reflux esophagitis, malaise, jaundice, skin lesion, nausea, abdominal pain, intestinal polyp , urinary tract infection, and peripheral neuropathy. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Asklepion Pharmaceuticals LLC at 1-844-CHOLBAM or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

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

- Bile Salt Efflux Pump (BSEP) Inhibitors (e.g., cyclosporine): Avoid concomitant use; if concomitant use is necessary, monitor serum transaminases and bilirubin (7.1)
- Bile Acid Resins and Aluminum-Based Antacids: Take CHOLBAM at least 1 hour before or 4 to 6 hours (or at as great an interval as possible) after a bile acid binding resin or aluminum-based antacids. (2.3, 7.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: March 2015

Cholic Acid (Cholbam™)

Goal(s):

- To ensure appropriate use of cholic acid in patients with bile acid synthesis disorders (BASDs) due to a single enzyme defects (SEDs) or as an adjunct to patients with peroxisomal disorders (PD), including Zellweger spectrum disorders, who exhibit manifestations of liver disease, steatorrhea, or complications from decreased fat-soluble vitamin absorption.

Length of Authorization:

- Up to 12 months

Requires PA:

- Cholic acid

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Is this a request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to # 5
5. Is cholic acid prescribed by a hepatologist or pediatric gastroenterologist?	**Yes:** Go to # 6	**No:** Pass to RPh. Deny; not funded by the OHP.

Approval Criteria		
6. Has baseline hepatic function been assessed? *The manufacturer recommends providers to monitor AST, ALT, GGT, alkaline phosphatase, bilirubin, and international normalized ratio (INR) every month for the first 3 months of therapy, every 3 months for the next 9 months, every 6 months during the next 3 years and annually thereafter.[1]	**Yes:** Approve for 6 months. Document baseline hepatic function values (AST,ALT, Alk Phos, bilirubin) and date obtained:_____	**No:** Pass to RPh. Deny; medical appropriateness

	Renewal Criteria	
1. Has the patient's condition stabilized or improved as assessed by the prescribing provider?	**Yes:** Approve for 12 months. Document most recent hepatic function values and date obtained:_____	**No**: Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 11/19 (DM)
Implementation: TBD

1. Cholbam (cholic acid) capsules [Full Prescribing Information]. San Diego, CA: Retrophin, Inc. March 2015.