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Drug Use Research & Management Program  
OHA Division of Medical Assistance Programs  
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College of Pharmacy

### Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Thursday, June 4<sup>th</sup>, 2020 1:00 - 5:00 PM

Remote Meeting via Zoom platform

#### MEETING AGENDA

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

#### I. CALL TO ORDER

- |         |  |  |
|---------|--|--|
| 1:00 PM | <ul style="list-style-type: none"> <li>A. Roll Call &amp; Introductions</li> <li>B. Conflict of Interest Declaration</li> <li>C. Approval of Agenda and Minutes</li> <li>D. Department Update</li> </ul> | <ul style="list-style-type: none"> <li>R. Citron (OSU)</li> <li>R. Citron (OSU)</li> <li>R. Citron (OSU)</li> <li>T. Douglass (OHA)</li> </ul> |
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1:15 PM	II. CONSENT AGENDA TOPICS	Chair
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- A. Quarterly Utilization Reports
- B. P&T Annual Report
- C. Acne Class Update with Akliel® (trifarotene) New Drug Evaluation
- D. Antiepileptics Class Update with Xcopri® (cenobamate) New Drug Evaluation
- E. Fluoroquinolone Drug Use Evaluation
- F. Oral Diuretics Class Update
- G. Orphan Drug Policy Updates
  - 1. Crysvida® (burosumab-twza)
  - 2. Brineura® (cerliponase alfa)
  - 3. Reblozyl® (luspatercept)
  - 4. Public Comment

#### III. DUR ACTIVITIES

- |         |   |  |
|---------|---|--|
| 1:20 PM | <ul style="list-style-type: none"> <li>A. ProDUR Report</li> <li>B. RetroDUR Report</li> <li>C. Oregon State Drug Review               <ul style="list-style-type: none"> <li>1. CGRP Antagonists in Migraine Prophylaxis</li> <li>2. Evidence for Drugs that are Heavily Marketed</li> </ul> </li> </ul> | <ul style="list-style-type: none"> <li>R. Holsapple (DXC)</li> <li>D. Engen (OSU)</li> <li>K. Sentena (OSU)</li> </ul> |
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#### IV. DUR OLD BUSINESS





## Oregon Pharmacy and Therapeutics Committee – Appointed members

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

## Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Thursday, February 06, 2020 1:00 - 5:00 PM

DXC Conference Room

4070 27th Ct. SE

Salem, OR 97302

MEETING AGENDA

**MEETING MINUTES**

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

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

**Members Present by Phone:** Megan Herink, PharmD

**Staff Present:** Roger Citron, RPh; Richard Holsapple, RPh; Deanna Moretz, PharmD; Sarah Servid, PharmD; Sara Fletcher, PharmD; Kathy Sentena, PharmD; Dee Weston; Trevor Douglass, DC, MPH; Brandon Wells; Jennifer Bowen;

**Audience:**

Will Lai, Xeris Pharmaceuticals\*; Jan Song, Xeris Pharmaceuticals; Anthony Mckenzie, OHSU; Suzanne Hensely, Xeris Pharmaceuticals; Kerri Miller, Blueprint Medicines; Ken Orr, Global Blood Therapeutics; Anthony Wheeler, Eli Lilly\*; Roy Lindfield Sunovion; Venus Holder, Eli Lilly; Doug Buriani, Sobi; BobbiJo Duim, BMS; Tracy Meeks, Vertex Pharmaceuticals; Garrett Funston, OHSU; Hiten Patadia, Otsuka; Rick Dabner, Alnylam Pharmaceuticals\*; Margaret Olmon, Abbvie\*; Samantha Shepard, CCO Oregon; Katie Scheelar, Moda; Lori McDermott, Supernus;

(\* ) 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. The Committee elected Jim Slater as the chair and Tracy Klein as the vice chair
- D. Approval of November 2019 minutes presented by Mr. Citron  
**ACTION: Motion to approve, 2<sup>nd</sup>, all in favor**
- E. Department and legislative update provided by Trevor Douglass

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**II. OREGON ADMINISTRATIVE RULE CHANGES**

- A. Proposed Language for OAR 414-121-0111
- B. P&T Operating Procedures  
Ms. Weston presented the proposed amendments to OAR 414-121-0111

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**III. CONSENT AGENDA TOPICS**

- A. P&T Methods for Quality Assessment of Evidence
- B. Immunosuppressants Literature Scan
- C. Diabetes, Insulins Literature Scan
- D. Jeuveau™ (prabotulinumtoxinA-xvfs) Abbreviated Drug Review
- E. Vyleesi™ (bremelanotide) Abbreviated Drug Review

**Recommendation:**

1. Make no changes to the preferred drug list (PDL) based on clinical evidence
2. Designate prabotulinumtoxinA-xvfs and bremelanotide as not covered
3. Evaluate comparative drug costs in executive session

**ACTION: Motion to approve, 2<sup>nd</sup>, all in favor**

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**IV. DUR ACTIVITIES**

- A. Quarterly Utilization Reports – Mr. Citron presented the Utilization Report
- B. ProDUR Report - Mr. Holsapple presented the ProDUR report
- C. RetroDUR Report – Mr. Citron presented the RetroDUR Report
- D. Oregon State Drug Reviews
  1. Pearls and Pitfalls of Clinical Practice Guidelines
  2. Update on Recent Guidance and Safety Alerts for Opioid Use in Non-Cancer PainDr. Sentena presented two recently published newsletters, thanked the Committee for reviewing the draft versions and solicited ideas for future newsletters

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## V. DUR NEW BUSINESS

### A. Orphan Drug Policy

Dr. Servid presented the policy proposal and proposed PA criteria

**ACTION:** The Committee recommended implementing the proposed PA criteria after amending to add a question requiring the medication be prescribed by or in consultation with an appropriate specialist for the condition to the initial approval criteria

**Motion to approve, 2<sup>nd</sup>, all in favor**

### B. Opioid Literature Scan and Prior Authorization Update

Dr. Servid presented the literature scan and proposed updates to the PA criteria for short- and long-acting opioids to prevent harm from abrupt discontinuation and reinforce a shared patient and provider decision for appropriate dosage reduction

**ACTION:** The Committee recommended implementing the proposed changes to the PA criteria after amending to remove the question requiring the provider to attest that the opioid will not be prescribed with a concurrent sedating medication

**Motion to approve, 2<sup>nd</sup>, all in favor**

### C. Febuxostat Prior Authorization Update

Dr. Sentena presented the proposal to add a requirement to the PA criteria that the patient has been assessed for CV risk and the benefits outweigh the risks.

**ACTION: Motion to reject, 2<sup>nd</sup>, 7 in favor, 1 opposed**

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## III. PREFERRED DRUG LIST NEW BUSINESS

### A. Diabetes, Glucagon Class Review

Dr. Sentena presented the proposal to:

1. Create a PDL class for the glucagon products
2. Evaluate costs in executive session

**ACTION: Motion to approve, 2<sup>nd</sup>, all in favor**

### B. Xenleta™ (lefamulin) New Drug Evaluation

Dr. Herink presented the proposal to make oral lefamulin non-preferred in the miscellaneous antibiotic PDL class

**ACTION: Motion to approve, 2<sup>nd</sup>, all in favor**

C. Biologics for Autoimmune Conditions Class Update and New Drug Evaluations

Dr. Moretz presented the proposal to:

1. Update the PA criteria to reflect funding of treatment of moderate-to-severe hidradenitis suppurativa (HS) per Guideline Note 198 on the Prioritized List of Health Services
2. Modify the PA criteria to reflect updated indications and age ranges for specific biologic response modifiers
3. Evaluate comparative costs in executive session

**ACTION: Motion to approve, 2<sup>nd</sup>, all in favor**

D. Narcolepsy Agents Class Update with New Drug Evaluation

Dr. Servid presented the proposal to:

1. Update safety edits for narcolepsy drugs to incorporate modafinil, armodafinil, solriamfetol and pitolisant into a unified criterion
2. Evaluate comparative costs in executive session

**ACTION: Motion to approve, 2<sup>nd</sup>, all in favor**

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## VI. EXECUTIVE SESSION

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

**Members Present by Phone:** Megan Herink, PharmD

**Staff Present:** Roger Citron, RPh; Richard Holsapple, RPh; Deanna Moretz, PharmD; Sarah Servid, PharmD; Sarah Fletcher, PharmD; Kathy Sentena, PharmD; Dee Weston; Trevor Douglass, DC, MPH; Brandon Wells; Jennifer Bowen;

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## VII. RECONVENE for PUBLIC RECOMMENDATIONS

A. Immunosuppressants Literature Scan

**Recommendation:** make all treatments preferred on the PMPDP

**ACTION: Motion to approve, 2<sup>nd</sup>, all in favor**

B. Diabetes, Insulins Literature Scan

**Recommendation:** make all forms of insulin lispro - except Admelog® - preferred on the PMPDP and to remove PA for insulin detemir pen

**ACTION: Motion to approve, 2<sup>nd</sup>, all in favor**

C. Diabetes, Glucagon Class Review

**Recommendation:** make GlucaGen®, glucagon emergency kit, and Baqsimi™ preferred and make Gvoke™ non-preferred on the PMPDP

**ACTION: Motion to approve, 2<sup>nd</sup>, all in favor**

D. Biologics for Autoimmune Conditions Class Update

**Recommendation:** make secukinumab preferred on the PMPDP

**ACTION: Motion to approve, 2<sup>nd</sup>, all in favor**

E. Narcolepsy Agents

**Recommendation:** make modafinil and armodafinil preferred on the PMPDP

**ACTION: Motion to approve, 2<sup>nd</sup>, all in favor**

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**IX. ADJOURN**

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**X. OHA Rules Advisory Committee**



**Pharmacy Utilization Summary Report: October 2018 - September 2019**

Eligibility	Oct-18	Nov-18	Dec-18	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Avg Monthly
Total Members (FFS & Encounter)	964,428	966,366	965,956	970,009	973,211	979,795	981,514	979,468	979,316	980,226	981,629	983,778	975,475
FFS Members	115,577	120,900	125,681	118,919	119,390	125,420	113,342	112,672	115,232	91,378	99,920	100,302	113,228
OHP Basic with Medicare	35,249	35,494	35,531	33,066	33,109	33,374	28,706	29,057	29,456	8,912	9,279	9,365	26,717
OHP Basic without Medicare	11,702	11,714	11,824	11,916	11,789	11,811	11,739	11,877	12,010	11,793	11,967	12,047	11,849
ACA	68,626	73,692	78,326	73,937	74,492	80,235	72,897	71,738	73,766	70,673	78,674	78,890	74,662
Encounter Members	848,851	845,466	840,275	851,090	853,821	854,375	868,172	866,796	864,084	888,848	881,709	883,476	862,247
OHP Basic with Medicare	41,471	41,476	41,372	43,801	43,841	43,822	48,472	48,276	48,107	68,815	68,626	68,722	50,567
OHP Basic without Medicare	62,281	62,113	61,913	61,991	61,974	61,949	62,066	61,919	61,721	61,928	61,667	61,560	61,924
ACA	745,099	741,877	736,990	745,298	748,006	748,604	757,634	756,601	754,256	758,105	751,416	753,194	749,757

Gross Cost Figures for Drugs	Oct-18	Nov-18	Dec-18	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	YTD Sum
Total Amount Paid (FFS & Encounter)	\$79,508,091	\$74,086,920	\$71,081,677	\$80,790,833	\$72,597,390	\$79,796,240	\$83,974,601	\$85,309,535	\$77,487,126	\$84,434,118	\$82,489,581	\$78,850,414	\$950,406,527
Mental Health Carve-Out Drugs	\$8,138,444	\$7,649,689	\$7,525,963	\$8,178,165	\$7,371,378	\$7,872,599	\$8,447,023	\$8,553,886	\$7,892,278	\$8,766,399	\$8,630,017	\$8,046,198	\$97,072,039
OHP Basic with Medicare	\$5,584	\$4,637	\$5,502	\$8,243	\$6,479	\$5,197	\$5,313	\$9,126	\$19,499	\$33,196	\$41,678	\$32,600	\$177,053
OHP Basic without Medicare	\$3,383,389	\$3,132,592	\$3,111,911	\$3,308,623	\$2,985,088	\$3,108,303	\$3,368,783	\$3,392,773	\$3,114,815	\$3,466,008	\$3,400,019	\$3,087,559	\$38,859,861
ACA	\$4,693,257	\$4,451,653	\$4,355,004	\$4,798,666	\$4,314,731	\$4,693,375	\$5,008,075	\$5,089,672	\$4,709,206	\$5,216,822	\$5,137,909	\$4,883,625	\$57,351,996
FFS Physical Health Drugs	\$3,066,981	\$2,656,234	\$2,671,043	\$3,149,848	\$2,628,466	\$2,866,531	\$2,879,529	\$2,928,429	\$2,761,419	\$2,784,022	\$2,712,855	\$2,479,913	\$33,585,268
OHP Basic with Medicare	\$292,188	\$244,574	\$241,618	\$255,721	\$220,074	\$257,718	\$252,451	\$210,691	\$212,526	\$53,974	\$54,883	\$55,001	\$2,351,418
OHP Basic without Medicare	\$936,448	\$814,596	\$777,823	\$1,027,448	\$877,313	\$953,040	\$913,628	\$976,770	\$992,605	\$1,090,022	\$977,794	\$864,560	\$11,202,045
ACA	\$1,712,861	\$1,467,421	\$1,527,713	\$1,744,092	\$1,418,666	\$1,541,019	\$1,579,942	\$1,598,131	\$1,436,002	\$1,522,607	\$1,534,083	\$1,428,035	\$18,510,571
FFS Physician Administered Drugs	\$1,829,438	\$1,516,168	\$1,335,321	\$1,913,929	\$1,961,560	\$1,748,589	\$1,448,587	\$1,525,530	\$1,849,022	\$1,148,504	\$1,203,495	\$1,465,578	\$18,945,723
OHP Basic with Medicare	\$411,838	\$441,764	\$308,689	\$554,014	\$498,232	\$488,756	\$368,758	\$388,516	\$340,349	\$125,472	\$175,576	\$175,827	\$4,277,790
OHP Basic without Medicare	\$601,271	\$134,561	\$129,694	\$330,123	\$519,480	\$235,158	\$248,854	\$242,006	\$562,170	\$191,130	\$158,786	\$570,026	\$3,923,258
ACA	\$470,684	\$585,397	\$568,530	\$615,390	\$559,836	\$570,030	\$414,542	\$467,329	\$563,376	\$353,571	\$486,646	\$397,524	\$6,052,854
Encounter Physical Health Drugs	\$54,156,156	\$50,053,366	\$48,453,530	\$53,556,251	\$48,758,696	\$54,659,823	\$57,490,888	\$57,954,484	\$52,005,953	\$56,705,122	\$55,835,831	\$53,806,241	\$643,436,341
OHP Basic with Medicare	\$262,717	\$254,909	\$268,236	\$320,613	\$266,975	\$307,860	\$299,947	\$360,284	\$566,464	\$771,707	\$714,357	\$732,681	\$5,126,752
OHP Basic without Medicare	\$14,202,996	\$13,151,735	\$12,793,773	\$13,539,999	\$11,979,850	\$13,354,332	\$14,401,566	\$14,580,939	\$13,239,739	\$13,894,323	\$13,437,514	\$12,775,632	\$161,352,398
ACA	\$39,049,457	\$36,026,959	\$34,815,080	\$38,924,465	\$35,821,410	\$40,326,796	\$42,115,076	\$42,372,814	\$37,611,141	\$41,397,900	\$41,090,808	\$39,682,894	\$469,234,802
Encounter Physician Administered Drugs	\$12,317,071	\$12,211,462	\$11,095,821	\$13,992,640	\$11,877,291	\$12,648,697	\$13,708,575	\$14,347,207	\$12,978,453	\$15,030,072	\$14,107,383	\$13,052,484	\$157,367,155
OHP Basic with Medicare	\$269,712	\$259,504	\$229,641	\$395,344	\$305,215	\$276,707	\$324,909	\$366,509	\$323,622	\$504,207	\$486,824	\$522,108	\$4,264,302
OHP Basic without Medicare	\$2,810,516	\$2,956,593	\$2,673,148	\$3,072,169	\$2,938,673	\$2,840,378	\$3,041,280	\$3,388,212	\$2,810,401	\$2,879,577	\$2,933,736	\$2,682,849	\$35,027,532
ACA	\$9,044,219	\$8,868,040	\$8,056,751	\$10,339,521	\$8,504,493	\$9,379,435	\$10,135,061	\$10,389,939	\$9,689,970	\$11,221,953	\$10,363,753	\$9,540,999	\$115,534,135

OHP = Oregon Health Plan

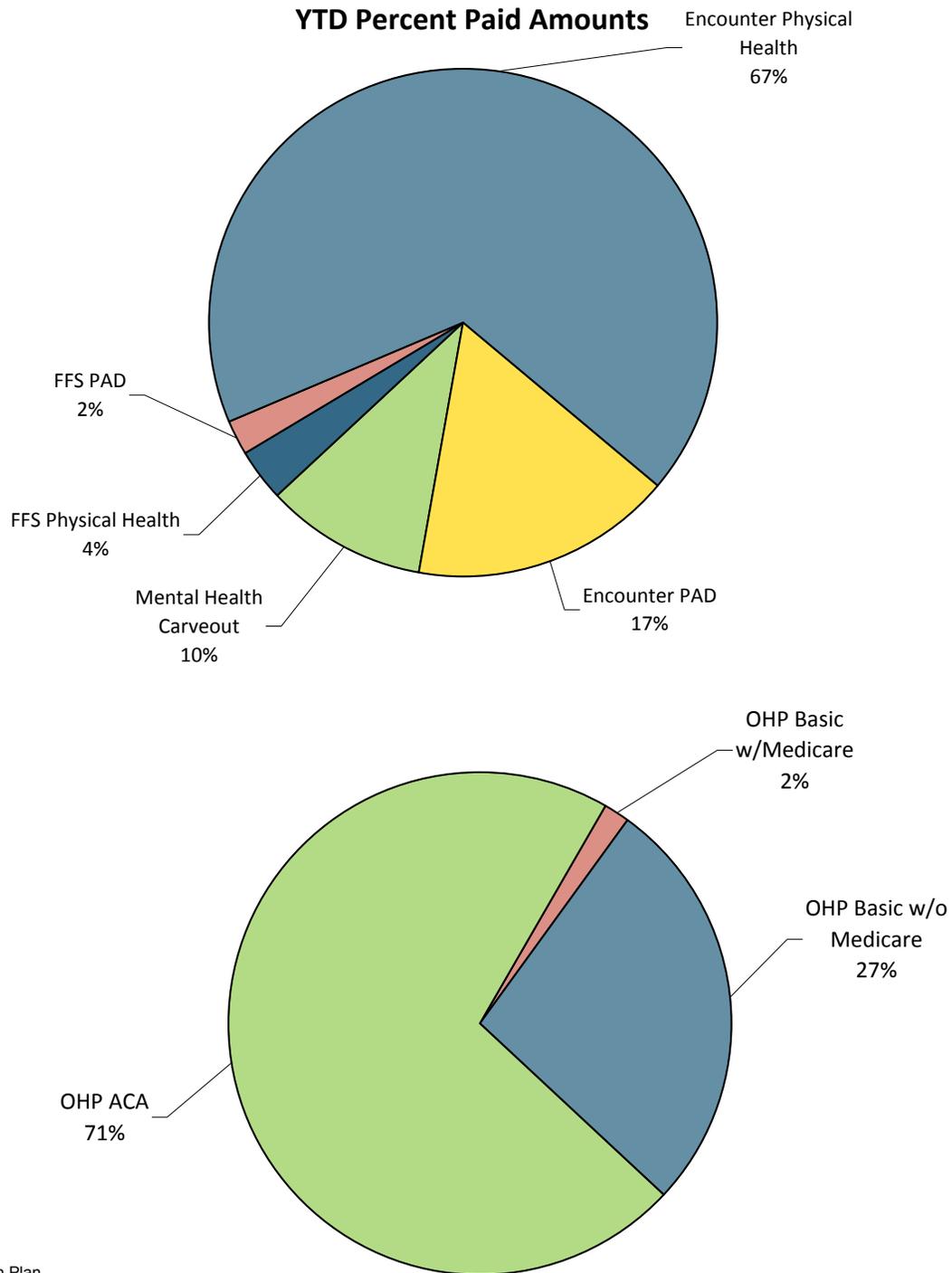
ACA = Affordable Care Act expansion

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

Last Updated: April 23, 2020



**Pharmacy Utilization Summary Report: October 2018 - September 2019**



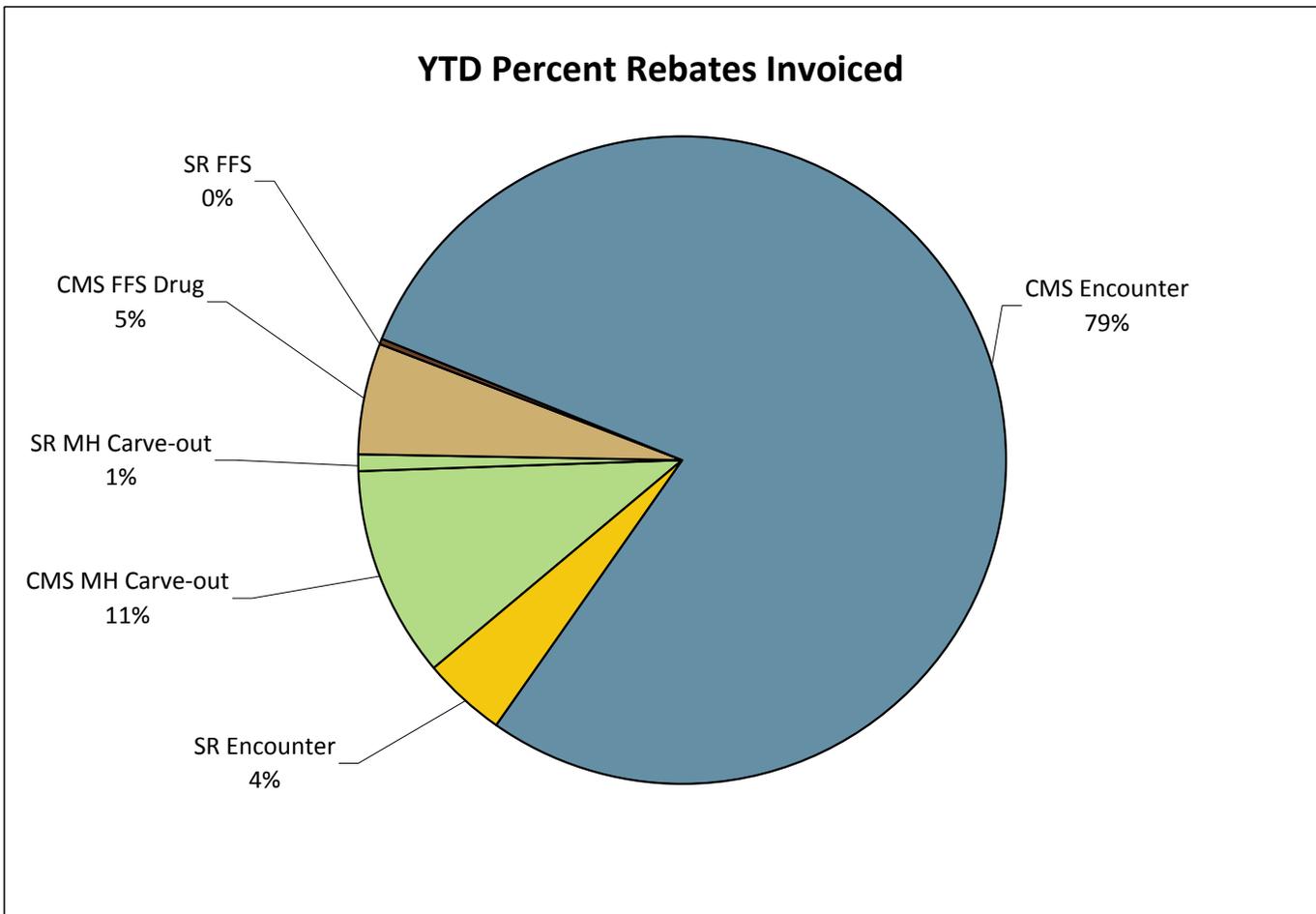
OHP = Oregon Health Plan  
ACA = Affordable Care Act expansion  
PAD = Physician-administered drugs  
Amount Paid on the Claim = 1) Ingredient Cost ((AAAC/NADAC/WAC) x Dispense Quantity) + Dispensing Fee.  
If Billed Amount is lower, pay Billed Amount, 2) - TPL amount



**Pharmacy Utilization Summary Report: October 2018 - September 2019**

Quarterly Rebates Invoiced	2018-Q4	2019-Q1	2019-Q2	2019-Q3	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	\$100,552,393	\$102,107,328	\$106,327,190	\$105,817,677	\$414,804,587
CMS MH Carve-out	\$10,075,720	\$11,124,217	\$11,401,532	\$11,200,239	\$43,801,709
SR MH Carve-out	\$654,824	\$1,065,433	\$1,120,134	\$1,156,919	\$3,997,311
CMS FFS Drug	\$5,418,111	\$6,293,370	\$6,013,182	\$5,078,781	\$22,803,443
SR FFS	\$232,205	\$247,106	\$304,068	\$301,351	\$1,084,730
CMS Encounter	\$81,455,319	\$79,499,062	\$81,444,558	\$83,238,531	\$325,637,470
SR Encounter	\$2,716,214	\$3,878,140	\$6,043,715	\$4,841,855	\$17,479,924

Quarterly Net Drug Costs	2018-Q4	2019-Q1	2019-Q2	2019-Q3	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	\$124,124,295	\$131,077,135	\$140,444,073	\$139,956,436	\$535,601,939
Mental Health Carve-Out Drugs	\$12,583,551	\$11,232,492	\$12,371,520	\$13,085,456	\$49,273,020
FFS Phys Health + PAD	\$7,424,871	\$7,728,446	\$7,075,267	\$6,414,234	\$28,642,818
Encounter Phys Health + PAD	\$104,115,873	\$112,116,196	\$120,997,286	\$120,456,746	\$457,686,101



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



**Pharmacy Utilization Summary Report: October 2018 - September 2019**

Gross PMPM Drug Costs (Rebates not Subtracted)	Oct-18	Nov-18	Dec-18	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	\$82.44	\$76.67	\$73.59	\$83.29	\$74.60	\$81.44	\$85.56	\$87.10	\$79.12	\$86.14	\$84.03	\$80.15	\$81.18
Mental Health Carve-Out Drugs	\$8.44	\$7.92	\$7.79	\$8.43	\$7.57	\$8.03	\$8.61	\$8.73	\$8.06	\$8.94	\$8.79	\$8.18	\$8.29
FFS Physical Health Drugs	\$26.54	\$21.97	\$21.25	\$26.49	\$22.02	\$22.86	\$25.41	\$25.99	\$23.96	\$30.47	\$27.15	\$24.72	\$24.90
FFS Physician Administered Drugs	\$15.83	\$12.54	\$10.62	\$16.09	\$16.43	\$13.94	\$12.78	\$13.54	\$16.05	\$12.57	\$12.04	\$14.61	\$13.92
Encounter Physical Health Drugs	\$63.80	\$59.20	\$57.66	\$62.93	\$57.11	\$63.98	\$66.22	\$66.86	\$60.19	\$63.80	\$63.33	\$60.90	\$62.16
Encounter Physician Administered Drugs	\$14.51	\$14.44	\$13.20	\$16.44	\$13.91	\$14.80	\$15.79	\$16.55	\$15.02	\$16.91	\$16.00	\$14.77	\$15.20

Claim Counts	Oct-18	Nov-18	Dec-18	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Avg Monthly
Total Claim Count (FFS & Encounter)	1,072,390	1,006,601	991,869	1,083,073	964,425	1,055,094	1,075,988	1,086,292	1,002,459	1,069,390	1,048,214	1,026,806	1,040,217
Mental Health Carve-Out Drugs	161,662	152,557	150,620	163,393	145,279	156,633	162,564	163,449	151,504	165,076	161,459	156,781	157,581
FFS Physical Health Drugs	58,522	54,918	53,755	60,179	53,706	58,697	56,935	56,878	51,160	43,068	42,330	41,593	52,645
FFS Physician Administered Drugs	15,129	13,809	14,247	16,083	13,326	14,867	13,929	14,596	13,260	12,236	11,778	11,225	13,707
Encounter Physical Health Drugs	723,932	679,603	668,553	729,141	650,897	712,776	727,106	733,875	675,695	725,889	708,029	698,191	702,807
Encounter Physician Administered Drugs	113,145	105,714	104,694	114,277	101,217	112,121	115,454	117,494	110,840	123,121	124,618	119,016	113,476

Gross Amount Paid per Claim (Rebates not Subtracted)	Oct-18	Nov-18	Dec-18	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Avg Monthly
Average Paid / Claim (FFS & Encounter)	\$74.14	\$73.60	\$71.66	\$74.59	\$75.28	\$75.63	\$78.04	\$78.53	\$77.30	\$78.96	\$78.70	\$76.79	\$76.10
Mental Health Carve-Out Drugs	\$50.34	\$50.14	\$49.97	\$50.05	\$50.74	\$50.26	\$51.96	\$52.33	\$52.09	\$53.11	\$53.45	\$51.32	\$51.31
FFS Physical Health Drugs	\$52.41	\$48.37	\$49.69	\$52.34	\$48.94	\$48.84	\$50.58	\$51.49	\$53.98	\$64.64	\$64.09	\$59.62	\$53.75
FFS Physician Administered Drugs	\$120.92	\$109.80	\$93.73	\$119.00	\$147.20	\$117.62	\$104.00	\$104.52	\$139.44	\$93.86	\$102.18	\$130.56	\$115.24
Encounter Physical Health Drugs	\$74.81	\$73.65	\$72.48	\$73.45	\$74.91	\$76.69	\$79.07	\$78.97	\$76.97	\$78.12	\$78.86	\$77.07	\$76.25
Encounter Physician Administered Drugs	\$108.86	\$115.51	\$105.98	\$122.44	\$117.34	\$112.81	\$118.74	\$122.11	\$117.09	\$122.08	\$113.21	\$109.67	\$115.49

Gross Amount Paid per Claim - Generic-Multi Source Drugs (Rebates not Subtracted)	Oct-18	Nov-18	Dec-18	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Avg Monthly
Generic-Multi Source Drugs: Average Paid / Claim (FFS & Encounter)	\$18.25	\$18.02	\$18.07	\$18.30	\$19.44	\$19.57	\$18.76	\$18.88	\$18.75	\$19.18	\$19.34	\$19.24	\$18.82
Mental Health Carve-Out Drugs	\$19.52	\$19.50	\$18.47	\$18.03	\$18.17	\$17.49	\$17.96	\$18.15	\$18.23	\$18.38	\$18.19	\$17.39	\$18.29
FFS Physical Health Drugs	\$16.42	\$16.66	\$15.89	\$16.63	\$16.85	\$17.47	\$17.94	\$17.17	\$17.58	\$19.08	\$19.76	\$19.17	\$17.55
Encounter Physical Health Drugs	\$18.05	\$17.74	\$18.13	\$18.50	\$19.94	\$20.23	\$19.02	\$19.18	\$18.96	\$19.39	\$19.61	\$19.71	\$19.04

Gross Amount Paid per Claim - Branded-Single Source Drugs (Rebates not Subtracted)	Oct-18	Nov-18	Dec-18	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Avg Monthly
Branded-Single Source Drugs: Average Paid / Claim (FFS & Encounter)	\$348.14	\$356.81	\$356.81	\$366.10	\$405.21	\$449.04	\$479.68	\$485.79	\$478.28	\$496.34	\$505.30	\$468.60	\$433.01
Mental Health Carve-Out Drugs	\$1,016.66	\$1,013.87	\$1,021.20	\$1,031.75	\$1,041.57	\$1,045.58	\$1,068.47	\$1,064.24	\$1,064.04	\$1,078.09	\$1,073.32	\$1,048.08	\$1,047.24
FFS Physical Health Drugs	\$152.18	\$141.52	\$149.12	\$162.40	\$154.01	\$163.05	\$171.73	\$180.98	\$196.31	\$265.18	\$264.04	\$234.42	\$186.25
Encounter Physical Health Drugs	\$345.74	\$356.04	\$353.93	\$362.39	\$407.52	\$455.95	\$486.35	\$491.63	\$479.04	\$482.19	\$491.67	\$455.95	\$430.70

Generic Drug Use Percentage	Oct-18	Nov-18	Dec-18	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Avg Monthly
Generic Drug Use Percentage	84.5%	85.2%	85.5%	85.7%	87.1%	88.1%	88.3%	88.5%	88.6%	88.7%	88.8%	88.3%	87.3%
Mental Health Carve-Out Drugs	96.9%	96.9%	96.9%	96.8%	96.8%	96.8%	96.8%	96.8%	96.8%	96.7%	96.7%	96.7%	96.8%
FFS Physical Health Drugs	73.5%	74.6%	74.6%	75.5%	76.6%	78.5%	78.8%	79.1%	79.6%	81.5%	81.9%	81.2%	77.9%
Encounter Physical Health Drugs	82.7%	83.5%	83.8%	84.0%	85.8%	87.0%	87.2%	87.3%	87.4%	87.3%	87.4%	86.9%	85.9%

Preferred Drug Use Percentage	Oct-18	Nov-18	Dec-18	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Avg Monthly
Preferred Drug Use Percentage	85.89%	85.81%	85.82%	85.82%	85.72%	85.72%	85.54%	85.52%	85.46%	85.42%	85.34%	85.26%	85.6%
Mental Health Carve-Out Drugs	73.82%	73.63%	73.67%	74.13%	73.91%	73.65%	73.66%	73.51%	73.26%	73.18%	73.17%	73.22%	73.6%
FFS Physical Health Drugs	95.68%	95.82%	95.79%	95.50%	95.43%	95.52%	95.23%	95.24%	95.48%	94.51%	94.59%	94.60%	95.3%
Encounter Physical Health Drugs	87.83%	87.77%	87.78%	87.66%	87.59%	87.59%	87.46%	87.47%	87.45%	87.65%	87.55%	87.43%	87.6%

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

Last Updated: April 23, 2020



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

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	LATUDA	Antipsychotics, 2nd Gen	\$6,559,884	16.6%	5,363	\$1,223	Y
2	INVEGA SUSTENNA	Antipsychotics, Parenteral	\$3,028,916	7.6%	1,528	\$1,982	Y
3	VRAYLAR	Antipsychotics, 2nd Gen	\$1,952,411	4.9%	1,686	\$1,158	Y
4	ABILIFY MAINTENA	Antipsychotics, Parenteral	\$1,666,629	4.2%	845	\$1,972	Y
5	REXULTI	Antipsychotics, 2nd Gen	\$1,549,686	3.9%	1,404	\$1,104	V
6	INVEGA TRINZA	Antipsychotics, Parenteral	\$803,496	2.0%	132	\$6,087	Y
7	TRINTELLIX	Antidepressants	\$592,701	1.5%	1,514	\$391	V
8	BUPROPION XL	Antidepressants	\$573,347	1.4%	27,948	\$21	V
9	ARISTADA	Antipsychotics, Parenteral	\$528,669	1.3%	249	\$2,123	Y
10	SAPHRIS	Antipsychotics, 2nd Gen	\$523,188	1.3%	795	\$658	Y
11	SERTRALINE HCL	Antidepressants	\$486,499	1.2%	48,138	\$10	Y
12	VIIBRYD	Antidepressants	\$480,855	1.2%	1,641	\$293	V
13	FLUOXETINE HCL	Antidepressants	\$465,805	1.2%	35,406	\$13	Y
14	DULOXETINE HCL	Antidepressants	\$458,878	1.2%	31,749	\$14	V
15	TRAZODONE HCL	Antidepressants	\$429,057	1.1%	42,095	\$10	
16	ATOMOXETINE HCL*	ADHD Drugs	\$390,721	1.0%	5,881	\$66	Y
17	PALIPERIDONE ER	Antipsychotics, 2nd Gen	\$372,435	0.9%	1,851	\$201	V
18	Inj, Nusinersen, 0.1mg	Physican Administered Drug	\$355,750	0.9%	2	\$177,875	
19	VENLAFAXINE HCL ER	Antidepressants	\$337,340	0.9%	1,966	\$172	V
20	BIKTARVY	HIV	\$311,870	0.8%	116	\$2,689	Y
21	RISPERDAL CONSTA*	Antipsychotics, Parenteral	\$300,570	0.8%	355	\$847	Y
22	ESCITALOPRAM OXALATE	Antidepressants	\$300,084	0.8%	28,903	\$10	Y
23	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	\$284,017	0.7%	25	\$11,361	Y
24	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	\$280,288	0.7%	20,056	\$14	
25	LAMOTRIGINE	Antiepileptics (oral & rectal)	\$266,638	0.7%	24,854	\$11	Y
26	ARIPIPRAZOLE	Antipsychotics, 2nd Gen	\$244,334	0.6%	15,853	\$15	V
27	TRIKAFTA*	Cystic Fibrosis	\$237,634	0.6%	24	\$9,901	N
28	LAMOTRIGINE ER	Antiepileptics (oral & rectal)	\$236,645	0.6%	2,206	\$107	V
29	CONCERTA*	ADHD Drugs	\$229,980	0.6%	739	\$311	N
30	CHOLBAM*	Bile Therapy	\$224,136	0.6%	3	\$74,712	N
31	VENLAFAXINE HCL ER	Antidepressants	\$210,032	0.5%	15,795	\$13	Y
32	AMITRIPTYLINE HCL*	Antidepressants	\$204,536	0.5%	14,615	\$14	Y
33	QUETIAPINE FUMARATE*	Antipsychotics, 2nd Gen	\$203,769	0.5%	17,321	\$12	Y
34	CITALOPRAM HBR	Antidepressants	\$190,795	0.5%	21,381	\$9	Y
35	LANTUS SOLOSTAR*	Diabetes, Insulins	\$188,373	0.5%	526	\$358	Y
36	Inj., Emicizumab-Kxwh 0.5 Mg	Physican Administered Drug	\$185,853	0.5%	7	\$26,550	
37	FETZIMA	Antidepressants	\$162,116	0.4%	394	\$411	V
38	Pegaspargase Injection	Physican Administered Drug	\$154,850	0.4%	3	\$51,617	
39	MIRTAZAPINE	Antidepressants	\$149,346	0.4%	9,678	\$15	Y
40	EPCLUSA*	Hepatitis C, Direct-Acting Antivirals	\$149,030	0.4%	9	\$16,559	Y
<b>Top 40 Aggregate:</b>			<b>\$26,271,163</b>		<b>383,056</b>	<b>\$9,773</b>	
<b>All FFS Drugs Totals:</b>			<b>\$39,600,443</b>		<b>664,677</b>	<b>\$615</b>	

\* 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



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

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	Inj, Nusinersen, 0.1mg	Physician Administered Drug	\$355,750	3.0%	2	\$177,875	
2	BIKTARVY	HIV	\$311,870	2.6%	116	\$2,689	Y
3	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	\$284,017	2.4%	25	\$11,361	Y
4	TRIKAFTA*	Cystic Fibrosis	\$237,634	2.0%	24	\$9,901	N
5	CONCERTA*	ADHD Drugs	\$229,980	1.9%	739	\$311	N
6	CHOLBAM*	Bile Therapy	\$224,136	1.9%	3	\$74,712	N
7	LANTUS SOLOSTAR*	Diabetes, Insulins	\$188,373	1.6%	526	\$358	Y
8	Inj., Emicizumab-Kxwh 0.5 Mg	Physician Administered Drug	\$185,853	1.6%	7	\$26,550	
9	Pegaspargase Injection	Physician Administered Drug	\$154,850	1.3%	3	\$51,617	
10	EPCLUSA*	Hepatitis C, Direct-Acting Antivirals	\$149,030	1.2%	9	\$16,559	Y
11	Epoetin Alfa, 100 Units Esrd	Physician Administered Drug	\$137,665	1.1%	513	\$268	
12	ALBUTEROL SULFATE HFA	Beta-Agonists, Inhaled Short-Acting	\$135,672	1.1%	3,371	\$40	Y
13	Etonogestrel Implant System	Physician Administered Drug	\$131,523	1.1%	219	\$601	
14	FLOVENT HFA	Corticosteroids, Inhaled	\$121,868	1.0%	723	\$169	Y
15	VYVANSE*	ADHD Drugs	\$121,427	1.0%	748	\$162	Y
16	HUMIRA(CF) PEN*	Biologics for Autoimmune Conditions	\$116,821	1.0%	34	\$3,436	Y
17	Ecuzumab Injection	Physician Administered Drug	\$110,233	0.9%	9	\$12,248	
18	NOVOLOG FLEXPEN	Diabetes, Insulins	\$109,040	0.9%	231	\$472	Y
19	GENVOYA	HIV	\$106,680	0.9%	38	\$2,807	Y
20	BUPRENORPHINE-NALOXONE*	Substance Use Disorders, Opioid & Alcohol	\$104,740	0.9%	1,893	\$55	Y
21	ELIQUIS	Anticoagulants, Oral and SQ	\$100,692	0.8%	290	\$347	Y
22	VIMPAT	Antiepileptics (oral & rectal)	\$97,771	0.8%	211	\$463	Y
23	TRUVADA	HIV	\$92,169	0.8%	78	\$1,182	Y
24	Factor VIII Recomb Novoeight	Physician Administered Drug	\$89,678	0.7%	3	\$29,893	
25	Injection, Pegfilgrastim 6mg	Physician Administered Drug	\$84,383	0.7%	32	\$2,637	
26	Inj Pembrolizumab	Physician Administered Drug	\$82,698	0.7%	41	\$2,017	
27	PULMOZYME	Cystic Fibrosis	\$82,560	0.7%	55	\$1,501	Y
28	Infliximab Not Biosimil 10mg	Physician Administered Drug	\$81,481	0.7%	71	\$1,148	
29	ENBREL SURECLICK*	Biologics for Autoimmune Conditions	\$80,315	0.7%	23	\$3,492	Y
30	XULANE	STC 63 - Oral Contraceptives	\$79,348	0.7%	492	\$161	
31	JAKAFI	Antineoplastics	\$79,317	0.7%	6	\$13,220	
32	ENBREL*	Biologics for Autoimmune Conditions	\$78,979	0.7%	11	\$7,180	Y
33	LANTUS	Diabetes, Insulins	\$78,582	0.7%	262	\$300	Y
34	Mirena, 52 Mg	Physician Administered Drug	\$77,858	0.6%	126	\$618	
35	Aflibercept Injection	Physician Administered Drug	\$72,170	0.6%	139	\$519	
36	HYDROXYPROGESTERONE CAPROAT	Progestational Agents	\$72,148	0.6%	33	\$2,186	N
37	XIFAXAN*	Rifamycins	\$70,420	0.6%	38	\$1,853	
38	VIGABATRIN	Antiepileptics (oral & rectal)	\$70,113	0.6%	12	\$5,843	N
39	XYREM	STC 47 - Sedative Non-barbiturate	\$69,950	0.6%	7	\$9,993	N
40	OPSUMIT*	Pulmonary Arterial Hypertension Oral and Inhale	\$69,802	0.6%	7	\$9,972	N
<b>Top 40 Aggregate:</b>			<b>\$5,127,597</b>		<b>11,170</b>	<b>\$12,168</b>	
<b>All FFS Drugs Totals:</b>			<b>\$11,978,512</b>		<b>157,935</b>	<b>\$632</b>	

\* 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

# Pharmacy & Therapeutics Committee Annual Report October 2017-September 2018

## Executive Summary

The 11-member Pharmacy and Therapeutics (P&T) Committee is responsible for advising the Oregon Health Authority (OHA) on the implementation of the fee-for-service retrospective and prospective programs and on the Practitioner-Managed Prescription Drug Plan. As a result of the P&T Committee's recommendations during FFY 2018, the OHA reimbursed pharmacies \$125,230,700. The total cost avoidance for the P&T-associated programs was calculated to be \$24,481,995. Savings were garnered through Drug Use Review (DUR) activities, Preferred Drug List (PDL) administration, Prior Authorization Criteria (PA) and Quantity Limits (QL). Details of the P&T recommendations and these highly successful programs are discussed in detail in the following annual report.

## Acronyms

- CMS** – Centers for Medicare & Medicaid Services
- DERP** – Drug Effectiveness Review Project
- DUR** – Drug Use Review
- DURM** – Drug Use Research & Management Program
- DXC** – DXC Technology
- FDB** – First Databank
- FFS** – Fee-For-Service
- FFY** – Federal Fiscal Year
- MMIS** – Medicaid Management Information Systems
- OAR** – Oregon Administrative Rules
- OHA** – Oregon Health Authority
- P&T** – Pharmacy & Therapeutics Committee
- PA** – Prior Authorization
- PAD** – Practitioner Administered Drug
- PDL** – Preferred Drug List
- PMPDP** – Practitioner-Managed Prescription Drug Plan

**PMPM** – Per member per month

**POS** – Point of Sale

**ProDUR** – Prospective Drug Use Review

**QL** – Quantity Limits

**RetroDUR** – Retrospective Drug Use Review

**SR** – Supplemental Rebates

**SSDC** – Sovereign States Drug Consortium

## Scope and Purpose

The Pharmacy and Therapeutics (P&T) Committee is subject to multiple reporting requirements. Pursuant to Oregon Revised Statutes (ORS 414.382), the P&T Committee is directed to publish an annual report. The P&T Committee also serves as the federally mandated Drug Use Review (DUR) Board and is required to report retrospective drug use review (RetroDUR) and prospective drug use review (ProDUR) activities, state prescribing habits, and cost savings generated from these programs to the Centers for Medicare & Medicaid Services (CMS) annually. At various points, this report will restate, summarize and expand upon the [CMS annual report](#).

This report covers the 2018 federal fiscal year (October 1, 2017 through September 30, 2018) and provides an overview of the programs and activities of the P&T Committee; an assessment of the impact of interventions, criteria and standards; and an estimate of the cost savings generated as a result of these programs. A complete list of P&T Committee activities, reports, report methodology and related resources are contained within the appendices.

Not covered in this report are programs that were initiated prior to this reporting period and continue to provide significant financial and clinical benefits. There are over 130 drug classes in the fee-for-service (FFS) preferred drug list affecting over 1,700 unique drugs that have been reviewed by the P&T Committee. Over 100 unique clinical use criteria have been created and are being maintained. The maintenance of previous utilization controls and impact of past educational initiatives, although not detailed in this report, continue to provide quantifiable financial benefits and shape provider behavior beneficial to Medicaid members, the Oregon Health Authority (OHA), and the state.

## Organizational Structure

The P&T Committee is responsible for advising the OHA on the development and implementation of the criteria and standards used for the Medicaid fee-for-service (FFS) RetroDUR program, ProDUR program, and the Practitioner-Managed Prescription Drug Plan (PMPDP), also known as the FFS preferred drug list (PDL).

There are several contractors involved with the P&T Committees' activities. The Oregon State University College of Pharmacy, Drug Use Research & Management (DURM) program provides staff support for the P&T Committee. DURM develops the evidence-based reviews, drug use evaluations, policy evaluations and PDL analysis which inform the P&T Committee recommendations. DURM also assists with PDL development and maintenance. DXC administers the state's electronic monitoring system called the Medicaid Management Information Systems (MMIS), staffs the call center that responds to prior authorization (PA) requests, and invoices for rebates on behalf of the OHA. DURM assists DXC with implementing the edits and coding necessary to operationalize the P&T Committee recommendations that have been approved by the OHA. The Sovereign States Drug Consortium (SSDC) is a non-profit, multi-state, Medicaid purchasing pool that negotiates supplemental rebates with manufacturers on behalf of member states. These supplemental rebate offers are considered by the P&T Committee when making PDL recommendations. Finally, the OHA is a member of the Drug Effectiveness Review Project (DERP) which is a collaborative group of state Medicaid agencies that commission high-quality comparative effectiveness reviews. The DERP reports are summarized and presented to the P&T Committee by the DURM staff.

## Evidence Reviews

Reviews of the most recent medical literature are the foundation of the P & T Committee activities. The P&T Committee met six times during this reporting period. **Table 1** summarizes the body of work that was developed by the OSU College of Pharmacy DURM program and presented to the P&T Committee during the year. A sound review of the published evidence is the starting point for developing utilization controls. The Committee's recommendations informed the implementation of the OHA's retrospective and prospective DUR programs, utilization controls, PA criteria, quantity limits and other conditions for coverage. Utilization controls such as PA criteria and quantity limits recommended by the P&T Committee are intended to promote use of safe, appropriate and cost-effective prescription drug therapy. PA criteria are designed to support access to and use of medications as approved by the FDA and are evaluated periodically to ensure they are functioning as intended and not causing any unanticipated harms. Further details about utilization control policies and management are provided in the PDL & Utilization Management section below. Links to the agendas, reports, and recommendations to the OHA can be found in **Appendix A**.

Report Type	Number of Reports Presented
Class Reviews & Updates	22
Drug Use & Policy Evaluations	5
New Drug Evaluations	7
Drug Class Scans	9

**Table 1.** Summary of Reports presented to the Pharmacy and Therapeutics Committee during federal fiscal year 2018.

## Prospective Drug Use Review (ProDUR) Programs

Section [1927](#) of the Social Security Act requires Medicaid programs to have a ProDUR program. Utilization controls, an important element of a ProDUR program, represent the first phase of screening for prescription drug claims at the point-of-sale (POS). DXC is the OHA's pharmacy benefit administrator and is responsible for maintaining and processing Medicaid pharmacy claims through the POS system, which interfaces with MMIS. DXC, through its contract with First Databank (FDB), loads information and edits into the claims processing system on a weekly schedule. Before each prescription is filled at the pharmacy a review of drug therapy is performed by the pharmacist and then submitted electronically to the state's MMIS. The MMIS screens prescription drug claims to identify potential problems based on the alerts detailed in **Appendix B** such as therapeutic duplication, drug interactions, incorrect dosage or duration of treatment, drug allergy, and clinical misuse or abuse. These alerts offer pharmacists additional information and the opportunity to consult with patients and prescribers to optimize care.

Early Refill and Pregnancy/Drug Interaction are the only two ProDUR alerts currently set to deny claims for FFS Medicaid pharmacy claims. Additional ProDUR alerts are sent to pharmacies when they process claims, but do not result in denial or require action by the pharmacy. These alerts are informational and provide the pharmacy with notification of potential drug therapy problems, which may improve patient care. The cost savings associated with claims that were not dispensed after the early refill or pregnancy/drug interaction alerts were triggered was \$158,508 during FFY 2018. Cost savings were calculated based on claims that were cancelled after the alert and not reprocessed again at a later date. See **Appendix B** for a detailed ProDUR Program Activity summary.

## Retrospective Drug Use Review (RetroDUR) Programs

The RetroDUR Program is the second phase of screening prescription drug claims to identify opportunities to improve quality of care and fiscal stewardship after medications have been dispensed to patients. RetroDUR involves ongoing and periodic examination of claims data to identify patterns of fraud, abuse, gross overuse, or medically unnecessary care. RetroDUR programs may be associated with specific drugs or groups of drugs and are designed to implement corrective action when concerning drug utilization patterns are identified. RetroDUR interventions occur after dispensing of medication and are intended to alter future behaviors. Quantification of the success of these programs is less straightforward when compared to ProDUR, Preferred Drugs List, and other utilization controls.

The DURM group has developed several RetroDUR safety net programs. The Long-Acting Beta Agonist/Inhaled Corticosteroid (LABA/ICS) Safety Net program is one example that targets members with asthma or COPD who were denied a pharmacy claim without a subsequent claim for a therapeutic alternative. This situation was identified as a potential gap in care that could

be addressed by a RetroDUR provider notification program. Over the year, 24 providers were sent notifications alerting them to the lack of ongoing therapy. Although it is difficult to quantify the clinical impact on outcomes such as emergency department visits, the program reduces the chance a member will go without a needed medication.

Dose optimization programs are RetroDUR programs with more easily quantified benefits. For a variety of reasons, Medicaid members may end up on a drug regimen with an unexpectedly large quantity of low strength tablets that can be much more expensive and wasteful than optimal dosing. In some cases, medications are available as both tablets and capsules with significant differences in cost. Optimizing the dose or formulation can result in significant savings and can also improve patient experience of care by lowering the number of needed pills. A RetroDUR Dose Optimization program was designed to educate providers of the cost difference and allow the providers to make changes when clinically appropriate. Latuda® (lurasidone HCl) is an example of a drug identified for dose optimization. Latuda accounts for nearly 15% of the total FFS drugs costs and is generally taken once daily. Providers prescribing two or more tablets per day were informed of the potential cost savings if they would prescribe higher strength tablets. Another example of successful provider outreach and education was targeted at venlafaxine, which is available in both tablet and capsule form with significant difference in cost.

During the fiscal year faxes were sent to 238 prescribers requesting their consideration of dose optimization. This resulted in an estimated savings of \$628,109. Faxes were sent to an additional 1,118 prescribers asking them to consider prescribing venlafaxine capsules instead of tablets, which is estimated to have saved an additional \$646,267. Savings from dose optimization are inherently conservative as this estimate does not include cumulative costs associated with changes in prescribing practices or ongoing use of more cost-effective regimens.

Patient safety is another focus of the RetroDUR program. Some examples include: polypharmacy reviews (OAR 410-121-0033) and the Pharmacy Management Program (OAR 410-121-0135). The polypharmacy reviews identify duplicative or unnecessary prescriptions filled by a member and provide an opportunity to notify prescribers with recommendations to consider discontinuing unneeded medications. The polypharmacy reviews saved an estimated \$1,500 over the fiscal year. The Pharmacy Management Program identifies potential fraud or misuse of drugs by a beneficiary, as indicated by members using multiple pharmacies in a short timeframe. The Pharmacy Management Program requires selected beneficiaries to use a single pharmacy to fill all their prescriptions for up to 18 months, which allows the pharmacy to monitor services being utilized and reduce unnecessary or inappropriate utilization.

In addition to the DUR programs, educational initiatives were employed to inform and influence prescribing practices to ensure safety and effectiveness. Publication and distribution of educational information to prescribers and pharmacists in the form of newsletters, fax notifications and individualized lettering regarding the committee activities and the drug use

review programs were performed. Faxes inform pharmacies when initiatives and utilization control changes are being implemented and help avoid interruptions in therapy for their patients. Over the fiscal year, two informational notifications were faxed to all enrolled pharmacies and 3,372 targeted individual communications were sent to prescribers.

Additionally, seven Oregon State Drug Reviews were published:

<http://pharmacy.oregonstate.edu/drug-policy/newsletters>

A complete list of RetroDUR activities and number of interventions is available in **Appendix C** and on the P&T Committee website.

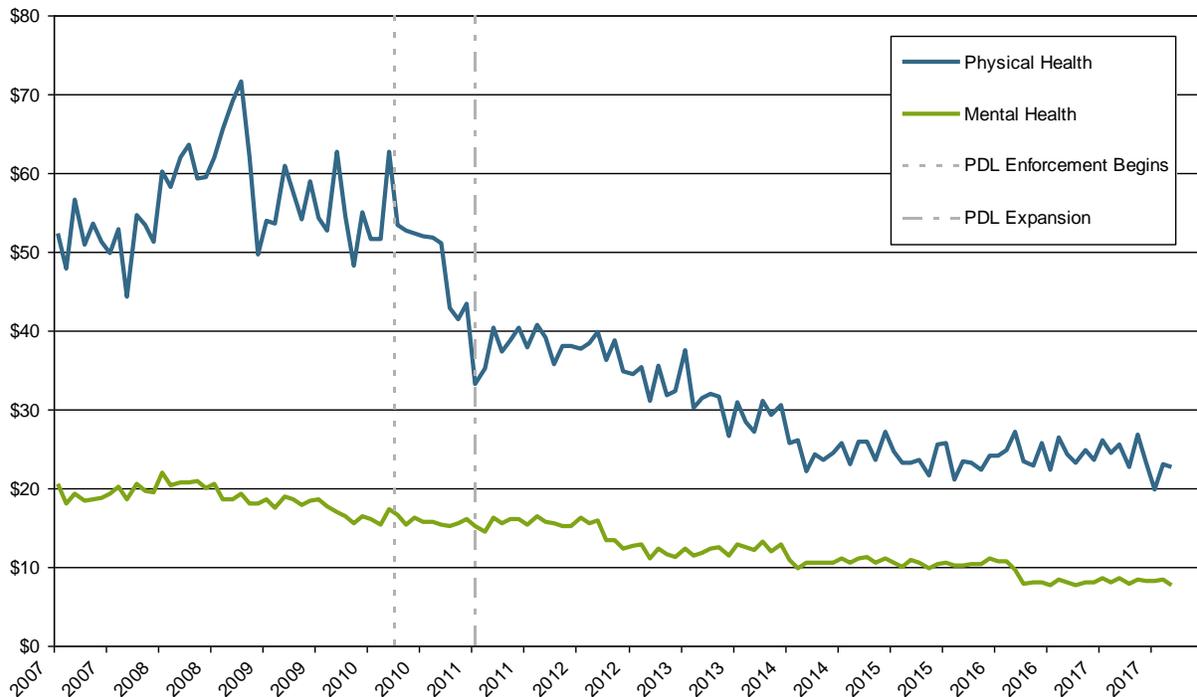
## Preferred Drug List & Utilization Management

The FFS Medicaid pharmacy program aims to achieve access to needed pharmaceuticals for Medicaid beneficiaries, administrative ease for providers, safety, and cost effectiveness. In order to manage FFS Medicaid prescription drug use, three primary tools are used: the PDL, PA Criteria and Quantity Limits (QL). The PDL contains a list of preferred drugs which have been determined by the P & T Committee to be the most safe and cost-effective. Drugs considered non-preferred require prescribers to contact the Oregon Pharmacy Call Center to obtain an authorization. Providers can obtain an authorization for diagnoses covered by the Prioritized List of Health Services by indicating they choose not to switch to the preferred drug. Dedicated clinical PA criteria are used for medications the OHA has determined require evaluation beyond simply being preferred or non-preferred. They ensure medications are being prescribed for funded conditions, are appropriate for the diagnosis for which they are being prescribed, or that less costly first-line therapies have been tried first. Quantity limits ensure the amounts prescribed are safe, appropriate and not wasteful. Working together, these three utilization management tools allow the OHA to provide safe, effective, and fiscally responsible drug benefits to members.

The PDL developed by the OHA is created using comparative evidence reviews of the medical literature (See **Table 1** and **Appendix A**). The P&T Committee also considers clinician and public input, as well as appropriate standards of care in the review process. Drugs and drug classes included on the PDL are evaluated by the P&T Committee and recommendations are made to the OHA for inclusion or removal from the PDL based on comparative safety, efficacy and cost-effectiveness. Drug cost is considered only after clinical recommendations are made and dedicated PA criteria are often developed as new classes are reviewed for inclusion on the PDL. Since implementation of the PDL in 2009 and the expansion of the classes included on the PDL in 2011, the cost per member for physical health drugs has markedly decreased (See **Figure 1**). With administration of the PDL and provider education, prescribers have become familiar with preferred medications and increasingly prescribe cost-effective medications. This is apparent in **Figure 1** below, which demonstrates decreasing costs after the PDL was implemented and subsequently expanded. However, it is important to note that other factors (such as demographic changes resulting from Medicaid expansion under the Affordable Care Act) could

also play a role in lowering costs. Continued maintenance and expansion of the PDL and development of utilization controls constitutes the bulk of the work performed and presented to the P&T Committee and generates the majority of the savings realized by the OHA.

**Figure 1:** *Gross Per-Member-Per-Month Prescription Drug Expenditures for Physical and Mental Health Drugs Over the Last Decade*



When making PDL decisions, cost is considered after evidence of safety and efficacy. Confidential federally mandated rebates, which are required of pharmaceutical manufacturers by Section 1927 of the Social Security Act as a condition for Medicaid coverage, are incorporated into the net cost considered by the P&T Committee. In addition, supplemental rebate offers, which manufacturers offer for some medications on top of the CMS federally mandated rebates, are negotiated on behalf of the OHA by the SSDC. Rebates can make the net cost of some brand name drugs comparatively cost-effective to alternative drugs in some classes. Supplemental rebates are not required to be offered by manufacturers in order for their medications to be considered for PDL preferred status, but they are considered in the net price. Both supplemental and federally mandated rebates are proprietary and confidential and cannot be disclosed to the public. Over the fiscal year, supplemental rebates collected by the state as a result of implementation and maintenance of the PDL was \$14,116,895. The physical health drugs accounted for the majority of these supplemental rebates totaling \$11,795,335. In contrast, the OHA is not allowed to enforce the mental health PDL (chapter 544, Oregon Laws

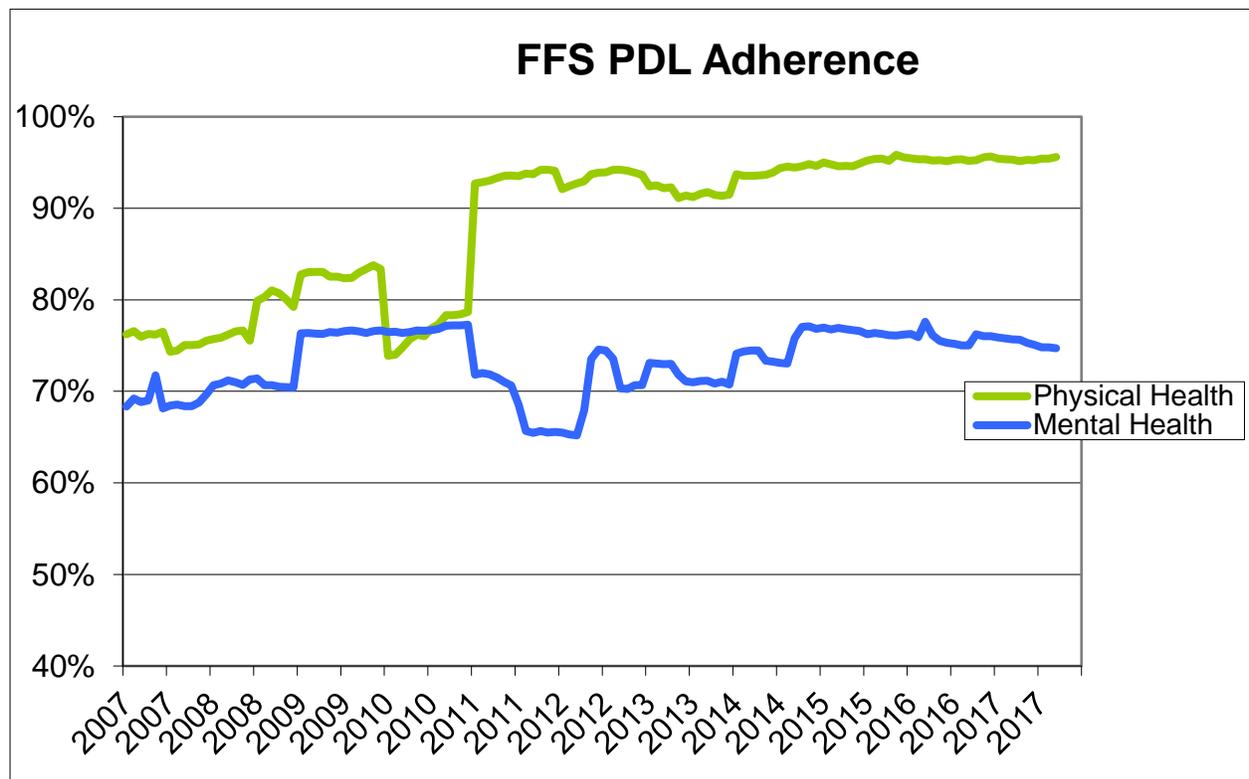
2019); as a result, the voluntary mental health PDL supplemental rebates accounted for a smaller total at \$2,321,560.

As illustrated in **Figure 2**, the ability to require PA for non-preferred physical health drugs resulted in a dramatic increase in the use of preferred agents - from 75% to 95% - after implementation of the PA for non-preferred agents. This was the driver of the significant savings illustrated in **Figure 1**. In contrast, the use of preferred mental health drugs has remained fairly flat (see **Figure 2**) due to a lack of a PA process for non-preferred agents.

Over the fiscal year, the Committee’s recommendations regarding drugs to be included on the PDL required changes to the PDL status of 53 drug products in the MMIS. Links to the current and historical versions of the PDL that were updated as a result of P&T Committee recommendations can be found in **Appendix D**.

Developing, revising, or removing existing PA criteria is an important role of the Committee. Over the year the P&T Committee recommended implementing, making substantive changes to, or retiring PA criteria 40 times and made more minor clerical changes to another 41 criteria. Many additional PA criteria were reviewed to ensure they remain reflective of current best evidence although no changes are made.

**Figure 2: Percent Use of Preferred Drugs for Physical Health Drugs (Enforced) and Mental Health Drugs (Not Enforced)**



The enforcement of quantity limits improves safety and patient outcomes by encouraging appropriate care and minimizing waste. They can be used to help prevent over use and dependence that can occur with sedative hypnotics, narcotic analgesics, benzodiazepines and certain migraine treatments. They are also used to ensure durations of therapy meet accepted standards of care, such as with certain antibiotics and proton pump inhibitors (PPIs). Quantity limits can also be used to assure doses do not exceed maximum safe levels. Initiatives to manage use of opioids with quantity limits and help address the ongoing prescription opioid epidemic has been a priority for the OHA and the Committee.

In select cases when brand name medications lose patent protection and generic alternatives are introduced into the market, the generic alternatives remain much more expensive than the net cost of the brand equivalent. In these cases, there is an opportunity to mandate continued use of the brand name drug until the cost of the generic alternatives drop. Careful analysis of the federally mandated rebates and comparative net cost of the alternatives is necessary to take advantage of this scenario. Since the selection of the medication being dispensed falls to the pharmacy (and they generally dispense the generic version if available), targeted communication is necessary to ensure pharmacies have adequate stock on hand and understand the departure from the general requirement to dispense generics. Pharmacies also need to have sufficient notice to know when this requirement will end so they can stock and begin to dispense the generic alternatives. Over the 2018 fiscal year three medications lost patent protection where this opportunity presented, resulting in \$139,763 in cost avoidance. In the past, these scenarios have resulted in savings exceeding \$15 million for one drug in a single year.

### Cost Avoidance Associated with the Utilization Management

Development and implementation of PA criteria and administration of the PDL encourages use of cost-effective therapies and limits costs due to inappropriate prescribing, waste, or abuse. The DURM group created a methodology to estimate cost avoidance attributable to PAs and the PDL. The methodology calculates savings by considering the ultimate therapy received by the member and the duration of cost avoidance. When payment for a claim is denied (e.g. denial due to a PA requirement or non-preferred status), all subsequent claims (paid and denied) for the member within the drug class are monitored. Cost avoidance is then calculated based on the initial claim (index event) and the final disposition of therapy within the drug class for a member.

Cost avoidance is categorized into one of several types based on the specific treatment recommendation and scenario. The cost avoidance categories are: deferred, therapeutic duplication, switched, add-on, discontinued, and other. A description of these types of cost avoidance can be found in **Appendix E**. Each cost avoidance type has a distinctive calculation for the duration of cost avoidance and the amount saved, based on the most likely clinical

treatment pathway. Factors considered for each cost avoidance type include: duration of eligibility for the fee for service program, enrollment into CCOs, maintenance drug indicator, cost of alternative therapy, and the number of paid and denied claims in the drug class.

The estimate of cost avoided over the fiscal year was \$22,743,398 in total drug expenditures by administration of PA criteria, PDL enforcement and quantity limits.

## Cost Benefit, Outcomes & Impact Assessment

The cost related to OHA's pharmacy contracts to support the P&T Committee must be accounted for when measuring the cost-benefit analysis of both the ProDUR and RetroDUR programs as well as PDL management.

DXC's and DURM's contracts are not solely devoted to the work of the P&T Committee as they provide additional services to assist the OHA. While it is impossible to calculate the cost of DXC's services that were directly associated with the functions of the P&T Committee, due to the nature of their contract and activities associated with MMIS, the portion of the DURM contract that was dedicated to supporting the P&T Committee work was estimated to be roughly 64% of their effort.

Since the DURM staff is almost exclusively staffed by pharmacists who provide clinical expertise to the OHA, the cost for their services is paid by 75% federal matching funds and 25% from state funds. Over the fiscal year, approximately \$788,906 was billed by DURM to the OHA for those clinical services, of which \$197,227 would have been state funds, with the remainder being federally funded.

The OHA also contracts with OHSU and is a member of the Drug Effectiveness Review Program (DERP). DERP is a collaborative group of state Medicaid agencies and other organizations that commission high-quality, evidence-based, comparative effectiveness reviews which are also presented to the P&T Committee. The cost to Oregon to participate in DERP for the fiscal year was \$95,500 which is paid with 50% state and 50% matching federal funds.

OHA is a member of the Sovereign States Drug Consortium, which is a CMS approved, state-administered, multi-state Medicaid supplemental drug rebate pool which negotiates supplemental rebate offers that are considered for PDL placement. Oregon paid \$13,245 total funds over the fiscal year to be a member of the SSDC and to take advantage of the supplemental rebates negotiated.

The cost benefit analysis of the ProDUR and RetroDUR programs should consider the total cost of the program, potential cost savings and avoidance, and the total cost of pharmacy benefits. The OHA reimbursed pharmacies \$125,230,700 over the fiscal year. Various vendor contracts (with specific calculations for DXC's contributions as described above) cost the state \$897,651 over the same period to provide services associated with the P&T Committee. These contract costs were approximately 0.72% of the total pharmacy expenditures. The total cost avoidance

for the P&T Committee-associated programs was calculated to be \$24,481,995, representing slightly more than 19% of total outpatient pharmacy expenditures. The return on the investment for P&T Committee-associated contracts was 27 to 1, demonstrating the value of services provided by all vendors involved.

## Appendices

### Appendix A – Materials Presented to the Pharmacy and Therapeutics Committee

#### Documents from October 2017 - September 2018

##### P &T Meetings

1. November 30, 2017 - [P&T Packet - Recommendations](#)
2. January 25, 2018 - [P&T Packet - Recommendations](#)
3. May 24, 2018 - [P&T Packet - Recommendations](#)
4. July 26, 2018 - [P&T Packet - Recommendations](#)
5. March 22, 2018 - [P&T Packet - Recommendations](#)
6. September 27, 2018 - [P&T Packet - Recommendations](#)

##### Class Reviews & Updates

1. [Multiple Sclerosis](#)
2. [Biologics for Autoimmune Conditions](#)
3. [PCSK9 Inhibitors](#)
4. [VMAT2 Inhibitors](#)
5. [Anti-Parkinson's Agents](#)
6. [Atopic Dermatitis](#)
7. [Bone Metabolism Agents](#)
8. [Oral Antipsychotics](#)
9. [Botulinum Toxins](#)
10. [Clostridium difficile Drugs](#)
11. [Glaucoma Drugs](#)
12. [Oral Fluoroquinolones](#)
13. [Topical Antibiotics](#)
14. [Asthma Biologics](#)
15. [Neuropathic Pain](#)
16. [Newer Diabetes Treatments](#)
17. [Oral Cystic Fibrosis Modulators](#)
18. [Benzodiazepines DERP Summary](#)
19. [Hepatitis C Direct-Acting Antivirals](#)
20. [Overactive Bladder Drugs DERP Summary](#)
21. [Pulmonary Hypertension Class Update](#)
22. [Vaginal Antibiotics Class Review](#)

##### Drug Use & Policy Evaluations

1. [Quetiapine](#)
2. [Use of Antipsychotics in Children](#)

3. [Gabapentin](#)
4. [Methadone](#)
5. [Benzodiazepines Policy Evaluation](#)

#### **New Drug Evaluations**

1. [Bevyxxa \(betrixaban, capsules\)](#)
2. [Keveyis \(dichlorphenamide, tablets\)](#)
3. [Luxtorna \(voretigene neparvovec-rzyl, intraocular suspension\)](#)
4. [Benlysta \(belimumab, injection\)](#)
5. [Radicava \(edaravone, injection\)](#)
6. [Aimovig \(erenumab-aooe, injection\)](#)
7. [Palynziq \(pegvaliase-pqpz, injection\)](#)

#### **Scans**

1. [Antidepressants](#)
2. [Class Scan: Asthma and COPD](#)
3. [Antiepileptics](#)
4. [Sedatives](#)
5. [ADHD Literature Scan](#)
6. [Antipsychotics Literature Scan](#)
7. [Botulinum Toxins](#)
8. [Oral Cystic Fibrosis Modulators](#)
9. [Pancreatic Enzymes Literature Scan](#)

#### **Newsletters**

1. [Nov 2017](#) - Marketing Claims of Newer Drugs and the Evidence
2. [Dec 2017](#) - Current Landscape of the Antidepressant Class: First Line Agents, Newer Agents, and Safety Risks
3. [Jan 2018](#) - What's New with Biologic Agents for Inflammatory Disease?
4. [Mar 2018](#) - Second Generation Antipsychotic Use in Major Depressive Disorder
5. [May 2018](#) - A Review of Implications of FDA Expedited Approval Pathways, Including the Breakthrough Therapy Designation
6. [Jul 2018](#) - Update on Treatment Options for Moderate to Severe Atopic Dermatitis
7. [Sep 2018](#) - Management Strategies for Patients with Prediabetes

## **Appendix B – ProDUR Summary**

The ProDUR review includes screening for potential drug therapy problems based on the following alerts:

DA Drug/Allergy Interaction: Triggers if there is an association between an ingredient and an allergy recorded in the recipient profile.

DC Inferred Disease Interaction: Triggers if there is a drug on the recipient's profile that is indicated for a disease state that interacts with the drug being filled.

DD Drug to Drug Interaction: Triggers if there is an interaction between the drug being filled and another drug on the recipient's profile.

ER Early Refill (Overutilization): Triggers if the drug being billed is too early based on previous billing and day supply. Allow filling when 80% of previous fill has been used.

HD High Dose: Triggers if the drug being billed, based on billed day supply, exceeds the maximum recommended daily quantity limit

ID Ingredient Duplication: Triggers if the drug being filled has a matching ingredient to another recently filled drug on the recipient's profile.

LD Low Dose: Triggers if the drug being billed, based on billed day supply, is below the minimum recommended daily quantity limit.

LR Late Refill (Underutilization): Triggers if the drug being filled is late in being refilled for the recipient.

MC Drug to Disease Interaction: Triggers if there is a disease Diagnosis (ICD-10) on the recipients claim profile that interacts with the drug being filled.

MX Maximum Duration of Therapy: Triggers if the day supply on the claim is greater than the maximum days value.

PA Pediatric and Geriatric Age Limits: Triggers if the age of the recipient is less than the minimum (pediatric) or greater than the maximum (geriatric) age for the drug being billed.

PG Pregnancy/Drug Interaction: Triggers if the drug being filled is contraindicated for use in pregnancy and the patient profile indicates that the patient may be pregnant.

TD Therapeutic Duplication: Triggers if the class of drug being billed matches the drug class of another recently filled medication on the recipient's profile.

**Early Refill and Pregnancy/Drug Interaction are the only two ProDUR alerts set to deny claims for FFS Medicaid pharmacy claims.**

### ***Cost Savings Estimates***

The Pro-DUR program currently relies on the following alerts for monitoring claims triggered by these alerts and controlling associated claim costs:

- Early Refill
- Pregnancy/Drug Interaction

### Early Refill Cost Savings Estimates

Starting January 13, 2013, a system enhancement went into production that required pharmacies to enter a Submission Clarification Code each time they were overriding an early refill ProDUR rejection. The accepted codes would help OHA and the P&T Committee to identify the reasons for the early refill. Accepted values in this field were as follows:

3= Vacation supply - The pharmacist is indicating that the cardholder has requested a vacation supply of the medication.

4= Lost prescription - The pharmacist is indicating that the cardholder has requested a replacement of medication that has been lost.

5= Therapy change - The pharmacist is indicating that the physician has determined that a change in therapy was required; either the medication was used faster than expected or a different dosage form is needed, etc.

6= Starter dose - The pharmacist is indicating that the previous medication was a starter dose and now additional medication is needed to continue treatment.

7= Medically necessary - The pharmacist is indicating that this medication has been determined by the physician to be medically necessary.

13=Payer-Recognized Emergency/Disaster Assistance Request-The pharmacist is indicating that an override is needed based on an emergency/disaster situation recognized by the payer.

14=Long Term Care Leave of Absence - The pharmacist is indicating that the cardholder requires a short-fill of a prescription due to a leave of absence from the Long Term Care (LTC) facility.

The cost savings due to claims that were not dispensed because of this alert, defined as being cancelled and then not being reprocessed again at a later date, are outlined in the table below.

Early Refill Cost Saving		
	ER Claims Cancelled	ER Cost Savings
October-17	20	\$1,905.47
November-17	36	\$12,578.99
December-17	22	\$1,173.78
January-18	13	\$1,063.67
February-18	37	\$6,353.46
March-18	17	\$1,424.57
April-18	490	\$96,755.21
May-18	47	\$9,832.61
June-18	17	\$5,153.52
July-18	32	\$6,322.42
August-18	17	\$4,197.94
September-18	12	\$6,342.94
<b>Total</b>	<b>760</b>	<b>\$153,104.58</b>

### Pregnancy/Drug Cost Savings Estimates

The cost savings due to claims that were not dispensed because of this alert, defined as being cancelled and then not being reprocessed again at a later date, are outlined in the table below.

<b>Pregnancy/Drug Interaction Cost Saving</b>		
	PG Claims cancelled	PG Cost Savings
October-17	0	\$0.00
November-17	0	\$0.00
December-17	0	\$0.00
January-18	0	\$0.00
February-18	2	\$174.64
March-18	0	\$0.00
April-18	7	\$3,891.43
May-18	0	\$0.00
June-18	0	\$0.00
July-18	2	\$1,336.98
August-18	0	\$0.00
September-18	0	\$0.00
<b>Total</b>	<b>11</b>	<b>\$5,403.05</b>

### Appendix C – RetroDUR Summary



RetroDUR\_Report\_2  
017-2018\_Q4.pdf

### Appendix D – PDL Changes

#### **PDLs from October 2017 - September 2018**

[Oregon Medicaid Preferred Drug List - January 1, 2018](#)

[Oregon Medicaid Preferred Drug List - March 1, 2018](#)

[Oregon Medicaid Preferred Drug List - July 1, 2018](#)

## Appendix E – Cost Avoidance Methodology Details

Cost avoidance is calculated based on the initial claim (index event) and the final disposition of therapy within the drug class for a member. The types of cost avoidance are: deferred, therapeutic duplication, switched, add-on, discontinued, and other. Each cost avoidance type has a distinctive calculation for the duration of cost avoidance and the amount saved, based on the most likely clinical treatment pathway.

**Deferred cost avoidance** includes claims for which the requested therapy is eventually approved and savings are calculated based on the time from the initial request to the first paid claim.

**Therapeutic duplication cost avoidance** is calculated when a drug is denied when there are already paid claims for an alternative in the same drug class.

**Switch cost avoidance** covers situations when a restricted access drug (PA required or non-preferred) is denied, but an alternative within the PDL class is subsequently paid. The difference in cost between the initial drug requested and the actual drug dispensed is the cost avoided.

**Add on therapy** is calculated when a drug is denied when there are already paid claims for an alternative that treats the same condition.

There are limitations to the cost avoidance methodology. The method is dependent upon detecting a denied claim. Members new to the Medicaid program or newly marketed medications are examples of situations that make it more difficult to adequately track and model potential savings. However, providers who have learned the FFS Medicaid PDL (or have learned to consult it) will prescribe preferred and unrestricted medications without first generating a denied claim for a drug requiring prior authorization. These types of long-term behavior modifications represent significant cost saving for the FFS program but are difficult to reliably quantify. Another limitation of the methodology occurs at the beginning and end of the reporting periods. Only costs avoided due to an initial denied claim during the reporting period are included. When an index event occurs immediately before the reporting period, there are savings associated with that event which are not summarized in the report. Likewise, when the initial denied claim occurs immediately before the end of the reporting period, the costs avoided after the end of the reporting period are not included. Significant savings go undetected with the methodology in the interest of conservative reporting. The methodology may also potentially inflate savings. For example, assuming a denied claim for a chronic medication would have continued to be filled throughout the reporting period, or until the member dis-enrolled could overestimate savings resulting from the intervention.

## Drug Class Update with New Drug Evaluation: Acne Drugs

**Date of Review:** June 2020

**Date of Last Review:** November 2018

**Generic Name:** Trifarotene

**Dates of Literature Search:** 08/03/2018 - 12/26/2019

**Brand Name (Manufacturer):** Akliel® (Galderma Laboratories, LP)

**Dossier Received:** no

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

### **Purpose for Class Update:**

The acne class has had one new approval, trifarotene cream, and several new product formulations since it was last reviewed in 2018. The purpose of this update is to evaluate new comparative evidence for trifarotene cream for the treatment of acne vulgaris and any new data on comparative efficacy or harms in the acne class since the previous update. Acne conglobata, acne fulminans, and severe cystic acne are covered conditions under the Oregon Health Plan (OHP).

### **Research Questions:**

1. What is the comparative efficacy and effectiveness of treatments for severe acne (topical agents of adapalene, adapalene/benzoyl peroxide, tretinoin, tazarotene, benzoyl peroxide, salicylic acid, dapson, azelaic acid, clindamycin, erythromycin, minocycline, sulfacetamide, trifarotene; oral systemic antibiotics of doxycycline, minocycline, tetracycline, azithromycin, erythromycin, clindamycin, trimethoprim, and sulfamethoxazole/trimethoprim; hormonal agents of oral contraceptives and spironolactone; and oral isotretinoin)?
2. What are the comparative harms of treatments for severe acne?
3. Are there subpopulations of patients in which a particular treatment for severe acne would be more effective or associated with less harm?

### **Conclusions:**

- There are no new high-quality clinical practice guidelines which have evaluated comparative efficacy and safety of treatments for acne vulgaris.
- Two high quality systematic reviews evaluated comparative efficacy and safety of oral isotretinoin with other acne vulgaris treatments. These reviews contain low- and very low-quality evidence due to various biases and methodological study limitations.
- There are no new randomized trials studying comparative efficacy and harms between treatment regimens for acne vulgaris.
- There is insufficient evidence to determine comparative efficacy and safety of treatments for severe acne.
- With the exception of oral isotretinoin, there is insufficient evidence to determine if any subpopulations would particularly benefit or be harmed by a particular treatment for severe acne.

- Trifarotene has moderate quality evidence due to study limitations to support its use in moderate acne vulgaris. Quality is limited by unclear selection bias, high attrition bias, and bias related to industry funding. Applicability is limited by lack of racial diversity in study population and limitations related to placebo control rather than active control. Number needed to treat of 6 to 10 for treatment success as defined by trial protocol.

#### **Recommendations:**

- Maintain non-preferred designation for trifarotene cream and other new single-source brand formulations on PDL given lack of high-quality data to support use in severe acne.
- No other PDL recommendations based on clinical evidence.
- Evaluate costs in the executive session.

#### **Summary of Prior Reviews and Current Policy**

- This drug class review is limited by the lack of high-quality evidence from high quality systematic reviews and guidelines which evaluate the comparative efficacy and safety of treatments for severe acne.
- There are also limited randomized controlled trials in the severe acne population and the majority of the trials are older with methodological and conflict of interest concerns.
- There is insufficient evidence to determine comparative efficacy and safety of treatments for severe acne.
- There is insufficient evidence to determine if any subpopulations would particularly benefit or be harmed by a particular treatment for severe acne.
- Though not of high methodological quality due to conflict of interest concerns, recent guidelines from the American Academy of Dermatology, European Academy of Dermatology and Venereology, and American Academy of Pediatrics recommend multiple treatment options for severe acne, all including isotretinoin. Other recommended treatments include combination therapy with systemic antibiotics and topical therapies such as benzoyl peroxide, retinoids, or topical antibiotics. Recommendations for treatment of mild to moderate acne generally includes the same therapies, either as monotherapy or in differing combinations, but isotretinoin is generally not recommended until acne is severe.
- Isotretinoin has substantial safety concerns compared to other medications for acne. There is an extremely high risk that severe birth defects will result if pregnancy occurs while taking isotretinoin. Because of the teratogenicity risk, it is approved for marketing only under a REMS program called iPLEDGE™.
- Prior authorization (PA) criteria for the Acne preferred drug list (PDL) class, includes federal legend topical medications that have an Food and Drug Administration (FDA) approved and OHA-funded indication for severe acne vulgaris and oral isotretinoin. Use is limited to funded conditions (**Appendix 6**).
- All single source brand agents are non-preferred and all other agents in the Acne PDL class are preferred.

#### **Background:**

Acne vulgaris (AV) is a chronic skin condition that affects approximately 50 million people in the United States.<sup>1</sup> It most commonly affects adolescents and young adults, but can continue into adulthood. Morbidity associated with acne can include permanent scarring, poor self-image, depression, and anxiety.<sup>1</sup> Acne vulgaris is characterized by noninflammatory open or closed comedones and inflammatory lesions.<sup>2</sup> These are generally located on the face, neck, back, chest, and upper arms.<sup>2,3</sup> Follicular hyperkeratinization, microbial colonization with *Cutibacterium acnes* (formerly *Propionibacterium acnes*), sebum production, and inflammatory factors involving innate and acquired immunity are all involved in the pathology of this condition.<sup>1,2</sup>

While there is no universal grading system, and as many as 18 different grading scales are used in the literature, classification of acne is commonly described as mild, moderate, or severe.<sup>1,3,4</sup> These are delineated by frequency of papules or pustules and presence and frequency of nodules, as well as presence of hyperpigmentation and erythema.<sup>3</sup> The Physician’s Global Assessment (PGA) is a 5-point scale (0-4) that was previously recommended by the FDA to evaluate success in clinical trials of acne vulgaris treatment.<sup>5</sup> The scale defines the skin as clear, almost clear, mild, moderate, and severe with corresponding descriptions for each score based on number of comedones, papules, pustules, nodules, cysts and overall amount of face involved.<sup>5</sup> More recently, the FDA has given industry guidance to use the Investigator’s Global Assessment (IGA) as an ordinal scale to assess overall severity.<sup>6</sup> The IGA is a 5- or 6-point scale (0-5) that grades hyperpigmentation and erythema as clear, almost clear, mild, moderate, severe, and very severe.<sup>6</sup> It should be used in conjunction with separate counting of inflammatory and noninflammatory lesions.<sup>6</sup>

Acne conglobata and acne fulminans are two forms of severe acne. Acne conglobata is a severe form of nodular acne that involves recurrent abscesses and communicating sinuses and often results in disfiguring scars.<sup>3</sup> Acne fulminans is a severe variant of inflammatory acne that presents with severe ulceration and occasionally the systemic symptoms of fever and arthralgia.<sup>3</sup> Assessment is done by physical exam and includes a pattern-diagnosis system that evaluates not only the presence and frequency of certain lesions, but also complications such as drainage, hemorrhage, pain and other factors like occupational disability, psychosocial impact, and failure of response to previous therapies.<sup>3</sup>

Treatment for acne may include a variety of agents such as topical medications (i.e., retinoids, benzoyl peroxide, topical antibiotics, salicylic acid, azelaic acid, sulfacetamide), systemic or topical antibiotics (i.e., doxycycline, minocycline, erythromycin, azithromycin, clindamycin, trimethoprim, dapsone), hormonal agents (i.e. oral contraceptives, spironolactone, antiandrogens), and oral isotretinoin.<sup>1,2,7</sup> Choice of treatment depends on severity of disease. Isotretinoin, which has an associated iPLEDGE REMS program, is specifically FDA-approved for severe recalcitrant nodular acne and recommended for severe acne.<sup>2,7</sup> Other treatments for severe acne usually include combination therapy with multiple classes of medications which can also be used for mild or moderate acne.<sup>2,7</sup> These classes of medications are well-established and all have been FDA-approved for many years.

Clinically meaningful outcomes for acne assessment include quality of life (QoL) and symptom reduction as demonstrated by decreased lesion counts or lessened acne severity. There are no QoL assessment tools recommended in the FDA guidance to industry<sup>6</sup>, nor was it included in the current new drug evaluation. Development and validation of a patient reported outcome measure for assessing acne treatment in the clinic is an identified research gap.<sup>1</sup> Though there seems to be no universally determined minimal clinically important difference for these outcomes, a consensus view of the authors of the European Evidence-Based Guidelines for Treatment of Acne suggested a minimal clinically important difference of 10% or greater reduction in lesion count as an efficacy outcome.<sup>8</sup> A final IGA assessment of 0 to 1 (clear to almost clear) and at least a 2-grade improvement from baseline is defined by the FDA as a clinically meaningful outcome.<sup>6</sup>

Prior authorization (PA) criteria for the Acne preferred drug list (PDL) class, includes federal legend topical medications that have FDA approval and an OHA-funded indication for severe acne vulgaris and oral isotretinoin. Use is limited to funded conditions in the OHP (**Appendix 6**).

**Table 1:** Acne class prior authorization requests

Time Period	Medication request number	Approval number	Denial number
4 <sup>th</sup> Quarter 2019	99 (1 cancelled)	50 (51%)	48 (48%)
3 <sup>rd</sup> Quarter 2019	39	26 (67%)	12 (31%)
2 <sup>nd</sup> Quarter 2019	71	45 (63%)	26 (37%)
1 <sup>st</sup> Quarter 2019	101 (1 cancelled)	50 (50%)	50 (50%)

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**Methods:**

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

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

**Systematic Reviews:**

After review, 2 systematic reviews were excluded due to poor quality<sup>9,10</sup> (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).

**Cochrane-Oral isotretinoin for acne**

The safety and efficacy of oral isotretinoin for acne vulgaris was assessed in a 2018 Cochrane review.<sup>11</sup> Thirty-one RCTs (n=3836) of patients aged 12-55 years with mild to severe acne were included.<sup>11</sup> Oral isotretinoin was compared to placebo and other therapies for acne vulgaris.<sup>11</sup> These trials were conducted in Asia, Europe, and North America, and outcomes were measured between weeks 8-32 of therapy.<sup>11</sup> All studies but three had a high risk of bias in at least one domain, and 12 of 16 studies were funded by pharmaceutical companies.<sup>11</sup> Additionally, 8 nonrandomized studies were included in the safety data for reporting serious adverse effects.<sup>11</sup>

Three studies (n=400) were included to assess a primary outcome of efficacy of oral isotretinoin versus a combination of oral antibiotics plus topical therapy in patients with moderate to severe acne.<sup>11</sup> Outcomes were assessed at the end of 20 to 24 weeks of treatment.<sup>11</sup> Investigator-assessed inflammatory lesion count was no different between isotretinoin versus comparator groups [Relative risk (RR) 1.01; 95% Confidence interval (95% CI), 0.96 to 1.06; n=400; 3 studies], though isotretinoin may slightly improve acne severity by the physician's global evaluation (RR 1.15; 95% CI, 1.00 to 1.32; n=351; 2 studies).<sup>11</sup> Risk of less serious side effects was higher with isotretinoin (RR 1.67; 95% CI 1.42 to 1.98; n=351; 2 studies). The severe side effect of Stevens-Johnson syndrome was seen once in an isotretinoin patient (RR 3.00; 95% CI, 0.12 to 72.98; n=400; 3 studies).<sup>11</sup> These outcomes were all from low- or very low-quality evidence.<sup>11</sup>

Another primary efficacy outcome involved treatment response based on differing oral isotretinoin doses (**Table 2**).<sup>11</sup> All outcomes were graded as low-quality evidence.<sup>11</sup> Heterogeneity in the studies precluded a meta-analysis of alternative dose regimens of isotretinoin.<sup>11</sup>

**Table 2.<sup>11</sup> Isotretinoin Dose Response**

Study/Doses	Result	Time of assessment
Study 1, severe acne (n=154) <ul style="list-style-type: none"> <li>• 0.05 mg/kg/d</li> <li>• 0.1 mg/kg/d</li> <li>• 0.2 mg/kg/d</li> </ul>	Decrease in total inflammatory lesion count <ul style="list-style-type: none"> <li>• 79%</li> <li>• 80%</li> <li>• 84%</li> </ul>	20 weeks
Study 2, severe acne (n=150) <ul style="list-style-type: none"> <li>• 0.1 mg/kg/d</li> <li>• 0.5 mg/kg/d</li> <li>• 1 mg/kg/d</li> </ul>	95% decrease in total inflammatory lesion count <ul style="list-style-type: none"> <li>• 58%</li> <li>• 80%</li> <li>• 90%</li> </ul>	20 weeks
Study 3, moderate acne (n=40) <ul style="list-style-type: none"> <li>• (A) 0.25-0.4 mg/kg/d continuous low-dose</li> <li>• (B) 0.5-0.7 mg/kg/d continuous conventional dose</li> <li>• (C) 0.5-0.7 mg/kg/d one week each month, intermittent regimen</li> </ul>	Decrease in total inflammatory lesion count <ul style="list-style-type: none"> <li>• [(A) vs. (C)], MD 3.72 lesions; 95% CI, 2.13 to 5.31</li> <li>• [(B) vs. (C)], MD 3.87 lesions; 95% CI, 2.31 to 5.43</li> </ul>	24 weeks

Abbreviations: MD = mean difference; mg/kg/d = milligrams per kilogram per day; 95% CI = 95% confidence interval

No serious adverse events were seen in studies comparing different dosing regimens of isotretinoin (n=906, 14 studies) during treatment duration of 12 to 32 weeks or during follow-up after treatment for up to 48 weeks.<sup>11</sup> Heterogeneity prevented meta-analysis of less serious adverse effects (n=858, 13 studies) such as skin dryness, hair loss, or itching.<sup>11</sup> Safety outcomes were graded as low- to very low-quality evidence.<sup>11</sup>

### British Journal of Dermatology-Efficacy and adverse events of oral isotretinoin for acne

The efficacy and safety of oral isotretinoin compared to alternative therapies or placebo in acne vulgaris was assessed in a 2018 British Journal of Dermatology review.<sup>12</sup> Eleven RCTs were included (n=760); only one RCT was assessed as low risk of bias in each of the 9 Cochrane criteria for study quality, while 3 qualified as low risk of bias overall.<sup>12</sup> The age range was 18.0 to 47.9 years, 20.5% of patients were female, and most patients had moderate to severe acne.<sup>12</sup> The trials had placebo control (n=1); active control with oral antibiotics including minocycline, erythromycin, tetracycline, dapsone, doxycycline, or azithromycin (n=7); alternative retinoid etretinate (n=1); and vitamin B complex (n=1).<sup>12</sup> Treatment ranged from 4 weeks to 6 months in duration.<sup>12</sup>

Seven of 11 trials showed statistical significance (p < 0.05 for the clinical endpoint of a 10% or greater reduction in acne lesion count) compared to the control group (placebo or active control).<sup>12</sup> All studies with placebo comparison (n=91) and those with alternative controls (etretinate, n=56; vitamin B complex, n=20) found a statistically and clinically significant improvement in patients treated with oral isotretinoin.<sup>12</sup> Results of isotretinoin compared to oral antibiotics (n=593) were more mixed, with only 3 of 7 studies showing statistical significance in favor of isotretinoin treatment.<sup>12</sup> Interpretation is also affected by the variety of antibiotic interventions used between different study protocols.<sup>12</sup>

Adverse reactions were grouped between studies by system given the variation in reporting structure between included trials (**Table 3**).<sup>12</sup> The authors rated the overall quality of evidence from this review as low.<sup>12</sup>

Table 3.<sup>12</sup> Isotretinoin Adverse Events

<b>Reaction</b>	<b>Adverse event frequency</b>	
	<b>Isotretinoin (n=364)</b>	<b>Control (all active and placebo) (n=384)</b>
Abnormal blood work	15	5
Dermatological reactions	487	227
Ear, nose, and throat	87	35
Gastrointestinal	15	34
Ophthalmological	54	17
Psychiatric	32	19
Other (headache, increased thirst, musculoskeletal pain, tender fingertips, unknown)	61	51
Total	751	388

**New Guidelines:**

No new clinical practice guidelines were identified.

**New Formulations or Indications:**

Tretinoin (Altreno™) 0.05% lotion was approved in August 2018 and is indicated for the topical treatment of acne vulgaris in patients 9 years and older.<sup>13</sup> It is a new dosage form of a previously marketed medication.

Minocycline (Amzeeq™) 4% foam was approved in October 2019 to treat inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients 9 years and older.<sup>14</sup> Administration via foam vehicle is a novel dosage form for this medication.

Tazarotene (Arazlo™) lotion was approved in January 2020 for the treatment of acne vulgaris in patients 9 years and older.<sup>15</sup> It is a new dosage form of a previously marketed medication.

Dapsone (Aczone®) 7.5% gel indication was expanded to 9 years of age in September of 2019.<sup>16</sup> This labeling change was not applied to the 5% formulation of this medication.

**Table 4. Description of Placebo-Controlled Studies of New Formulations**

<b>Study</b>	<b>Comparison</b>	<b>Population</b>	<b>Primary Outcome</b>	<b>Results</b>
<p>Gold et al<sup>17</sup></p> <p>2 identical studies (04 &amp; 05)</p> <p>MC, DB, VC, RCT, phase 3</p>	<p>FMX101 (4% minocycline foam) vs. Placebo vehicle</p> <p>2:1 randomization</p> <p>Self-application once daily x 12 weeks in evening</p> <p>Efficacy assessments at weeks 3, 6, 9, 12.</p> <p>Optional open-label continuation x 40 weeks</p>	<p>Age ≥9 years with moderate to severe facial acne.</p> <p>IGA score = 3 to 4; 20 to 50 inflammatory lesions; and 25 to 100 non-inflammatory lesions</p> <p>Study 04 n=466 Study 05 n=495</p>	<p><u>Coprimary endpoints</u></p> <p>(1) Absolute change in inflammatory lesion count from baseline to week 12.</p> <p>(2) Rate of IGA-assessed treatment success (score of 0 to 1 plus at least 2-grade improvement)</p>	<p><u>FMX101 vs vehicle</u></p> <p>Study 04 (1) -14.13 vs. -11.19; LSM difference 2.8; 95% CI 0.72 to 4.88; p=0.0083 (2) 8.09% vs. 4.77%; RR 1.72; 95% CI 0.73 to 4.05; p=0.2178</p> <p>Study 05 (1) -13.36 vs. -10.70; LSM difference 3.15; 95% CI 0.95-5.35; p=0.0051 (2) 14.66% vs. 7.89%; RR 1.88, 95% CI 1.02 to 3.46; p=0.0424</p>
<p>Tyring et al<sup>18</sup></p> <p>2 identical studies pooled</p> <p>MC, DB, VC, RCT</p>	<p>Tretinoin 0.05% lotion vs. Placebo vehicle</p> <p>1:1 randomization</p> <p>Self-application once daily x 12 weeks</p> <p>Efficacy assessments at weeks 4, 8, 12.</p>	<p>Age ≥9 years with moderate to severe facial acne.</p> <p>EGSS score of 3 (moderate) or 4 (severe) and lesion counts of 20 to 40 inflammatory lesions and 20 to 100 non-inflammatory lesions</p> <p>n=1640</p>	<p><u>Coprimary endpoints</u></p> <p>(1) Absolute change in mean inflammatory lesion count from baseline to week 12</p> <p>(2) Absolute change in mean non-inflammatory lesion count from baseline to week 12</p> <p>(3) Proportion of patients with at least 2-grade improvement in EGSS from baseline to week 12</p>	<p><u>Tretinoin 0.05% lotion vs. vehicle</u></p> <p>(1) LSM 52.1% vs. 41.0%; 95% CI NR; p&lt;0.001</p> <p>(2) LSM 46.1% vs. 29.9%; 95% CI NR; p&lt;0.001</p> <p>(3) NR</p>

Abbreviations: CI = confidence interval, DB = double blind, EGSS = Evaluator Global Severity Score, IGA = Investigator’s Global Assessment, LSM = least squares mean, MC = multicenter, NR = not reported; RCT = randomized controlled trial, RR = relative risk, VC = vehicle controlled

## New FDA Safety Alerts:

**Table 5. 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)
Clindamycin (topical)	Multiple	12/16/2019	Warnings and Precautions	Addition of breastfeeding caution
Dapsone	Aczone	5/18/2018	Adverse Reactions	Identified post-approval reactions for topical product: methemoglobinemia, rash (including erythematous rash, application site rash, and swelling of face (including lip swelling, eye swelling))
Isotretinoin	Absorica, multiple	5/2/2018	Warnings and Precautions	iPLEDGE program: prescriptions must be obtained no later than the “do not dispense to after” date. If not obtained, product must be returned to inventory.
Isotretinoin	Absorica, multiple	11/7/2019	Boxed Warning	Embryo-fetal toxicity and pregnancy contraindication reworded
Mequinol/Tretinoin	Solage	12/2/2019	Warnings and Precautions	Additions of warning of embryo-fetal toxicity, recommendations to use sunscreen and avoid potentially irritating products and weather extremes, and caution of potential to irritate eczematous skin and cause skin fissures added.

### Randomized Controlled Trials:

A total of 32 citations were manually reviewed from the initial literature search. After further review, 30 citations were excluded because of wrong study design (eg, observational)<sup>19-36</sup>, comparator (eg, no control or placebo-controlled)<sup>37-44</sup>, population<sup>45,46</sup>, or outcome studied (eg, non-clinical)<sup>47,48</sup>. The remaining 2 trials, which are placebo controlled, include new drug formulations, and are summarized in the table X above. Full abstracts are included in **Appendix 2**.

### NEW DRUG EVALUATION:

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

### Clinical Efficacy: Trifarotene

Trifarotene is a retinoid cream that is indicated for the topical treatment of acne vulgaris in patients 9 years of age and older.<sup>49</sup>

Trifarotene is an agonist of the retinoic acid receptors (RAR), with most affinity at the gamma subtype. This contrasts earlier topical retinoids, which target both the beta and gamma subtypes, though the clinical implication of this affinity is unknown.<sup>49,50</sup> Stimulation of RAR is associated with cell differentiation and reduction of inflammation. The exact mechanism for amelioration of acne is unknown.<sup>49</sup>

Trifarotene has been evaluated in two randomized, multicenter, parallel group, double-blind, vehicle-controlled trials with identical design to assess use for the treatment of moderate facial and truncal acne vulgaris [PERFECT 1 (NCT02566369), PERFECT 2 (NCT02556788)].<sup>49,50</sup> Patients aged 9 years and older were treated for up to 12 weeks with trifarotene cream or a placebo vehicle cream.<sup>49,50</sup> Patients were encouraged to moisturize either 1 hour before or after study treatment use.<sup>49,50</sup> Efficacy was assessed with a 5-point IGA for the face and 5-point PGA for the trunk; it is unclear why PGA was chosen for the truncal assessment.<sup>49,50</sup> Moderate acne scores 3 of 5 on these scales.<sup>49,50</sup> Treatment success required IGA/PGA scale achievement of both a minimum 2-point improvement from baseline AND a score of 0 (clear) or 1 (almost clear).<sup>49,50</sup> The IGA is a static evaluation recommended by the FDA for acne severity.<sup>6</sup> The co-primary endpoints related to the face at week 12 and were (1) percentage of subjects achieving IGA scale success as defined above, (2) mean absolute change in facial inflammatory lesion count from baseline, and (3) mean absolute change in facial non-inflammatory lesion count from baseline.<sup>49,50</sup> Co-secondary endpoints were the same indicators described previously but applied to assessment of the trunk and using the PGA scale.<sup>49,50</sup> FDA guidance recommends limiting efficacy assessment to the face, as it is the most frequent site of involvement.<sup>6</sup>

All primary and secondary endpoints were statistically significant but no 95% confidence intervals were provided for any endpoint.<sup>50</sup> (**Table 8**) PERFECT 1 had an overall IGA success of 29.4% for trifarotene, and 19.5% for placebo (ARR 9.9%/NNT 10) and PGA success of 35.7% for trifarotene, and 25.0% for placebo (ARR 10.7%/NNT 9).<sup>50</sup> Results for PERFECT 2 had higher IGA success rates in both groups, with 42.3% trifarotene and 25.7% placebo (ARR 16.6%/NNT 6) and PGA success of 42.6% trifarotene and 29.9% placebo (ARR 12.7%/NNT 8).<sup>50</sup> Changes in inflammatory lesions, while statistically significant, included high placebo response rates of 35.7 to 51.2% across the various primary and secondary endpoints.<sup>50</sup> These studies are of low quality, with limitations due to unclear selection bias in both trials and high attrition bias in PERFECT 1. Applicability is limited by low overall response rate in IGA, high placebo response rates in change of lesion count from baseline, and lack of diverse patient group.

#### **Clinical Safety:**

Trifarotene cream causes erythema, scaling, dryness, and stinging/burning, reactions tend to be worse early in therapy and lessen over time.<sup>49,50</sup> These adverse reactions were more common in the trifarotene group compared to the placebo group.<sup>49,50</sup> (**Table 6**) Patients will also experience more sensitivity to sun exposure during treatment.<sup>49</sup> Pregnant women were excluded from these phase III studies.<sup>49,50</sup> Fetal adverse effects have been found in animal studies using 800-times the systemic exposure represented in these studies, and oral retinoid use is known to result in birth defects.<sup>49</sup> There are no clinical data for use in lactation.<sup>49</sup> An open-label continuation study of 1 year duration had 2.9% of patients experience an adverse reaction which led to treatment discontinuation.<sup>49</sup>

**Table 6: Application Site Tolerability Reactions at Any Post Baseline Visit (p values not reported)<sup>49</sup>**

Face	Trifarotene N=1214			Vehicle cream (placebo) N=1194		
	Maximum Severity during Treatment (% of patients)			Maximum Severity during Treatment (% of patients)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Erythema	30.6	28.4	6.2	21	6.8	0.8
Scaling	37.5	27.1	4.9	23.7	5.9	0.3
Dryness	39	29.7	4.8	29.9	6.8	0.8
Stinging/Burning	35.6	20.6	5.9	15.9	3.8	0.5
Trunk	N=1202			N=1185		
Erythema	26.5	18.9	5.2	12.7	4.4	0.4
Scaling	29.7	13.7	1.7	13.2	2.6	0.1
Dryness	32.9	16.1	1.8	17.8	3.9	0.1
Stinging/Burning	26.1	10.9	4.3	9.2	2.2	0.5

**Comparative Endpoints:**

Clinically Meaningful Endpoints:

- 1) Acne severity
- 2) Number of inflammatory lesions
- 3) Number of non-inflammatory lesions
- 4) Quality of Life
- 5) Serious adverse events
- 6) Study withdrawal due to an adverse event

Primary Study Endpoint:

- 1) IGA response
- 2) Inflammatory lesions
- 3) Non-inflammatory lesions

**Table 7. Pharmacology and Pharmacokinetic Properties.**

Parameter	
Mechanism of Action	Retinoic acid receptor agonist of gamma subtype
Oral Bioavailability	Topical (n/a)
Distribution and Protein Binding	99.9% plasma protein bound
Elimination	Primarily feces
Half-Life	2-9 hours
Metabolism	CYP2C9, CYP3A4, CYP3C8, CYP2B6 (minor)



		<p>reachable for self-application)</p> <p>*criterion waived for 9-11 year olds due to rarity in this age group</p> <p><u>Exclusion Criteria:</u></p> <ul style="list-style-type: none"> <li>-severe acne</li> <li>- &gt;1 nodule on face</li> <li>- &gt;1 nodule on trunk</li> <li>-presence of acne cysts, beard, facial hair, or tattoos that could interfere with assessments</li> <li>-uncontrolled or serious medical condition</li> <li>-significantly abnormal lab values</li> <li>-drug sensitivities</li> <li>-pregnancy, lactation, or intent to conceive</li> </ul>		p<0.001 (95% CI NR)				<p><u>Setting:</u> Over 100 study sites across the United States, Canada, Russia, and Europe; all countries with a predominantly white population.</p>
<p>2. Tan et al<sup>49,50</sup></p> <p>Phase 3, DB, DB, RCT</p> <p>PERFECT 2</p> <p>NCT02556788</p>	<p>Identical to PERFECT 1 above</p> <p>1. Trifarotene cream 50 mcg/g once daily at bedtime x 12 weeks (T)</p> <p>2. Placebo vehicle cream once daily at bedtime x 12 weeks (P)</p> <p>Both groups instructed to cleanse skin before application. Moisturizer use was encouraged, but to be avoided 1 hr before or</p>	<p><u>Demographics:</u></p> <p>Age (mean, SD): 19.7 ± 6.3</p> <p>Male: 517 (42.7%)</p> <p>White: 1119 (92.3%)</p> <p>Skin phototype</p> <p>Type I: 73 (6%)</p> <p>Type II: 523 (43.2%)</p> <p>Type III: 481(39.7%)</p> <p>Type IV: 71 (5.9%)</p> <p>Type V: 33 (2.7%)</p> <p>Type VI: 31 (2.6%)</p> <p>Baseline lesions (Face) (mean ± SD)</p> <p>Inflammatory: 36.6 ± 13.84</p> <p>Noninflammatory: 50.9 ±25.83</p> <p>Baseline lesions (Trunk)</p>	<p><u>ITT:</u></p> <p>1. 602</p> <p>2. 610</p> <p><u>Attrition:</u></p> <p>1. 44 (7.3%)</p> <p>2. 37 (6.1%)</p>	<p><u>Primary Endpt (FACE) # (%):</u></p> <p><i>IGA success</i></p> <p>Trifarotene 255 (42.3)</p> <p>Placebo 157 (25.7)</p> <p>p&lt;0.001 (95% CI NR)</p> <p><i>Inflammatory lesions:</i></p> <p>Mean absolute Δ from baseline</p> <p>Trifarotene -24.2 (-66.2)</p> <p>Placebo -18.7 (-51.2)</p> <p>p&lt;0.001 (95% CI NR)</p> <p><i>Noninflammatory lesions:</i></p> <p>Mean absolute Δ from baseline</p> <p>Trifarotene -30.1 (-57.7)</p> <p>Placebo -21.6 (-43.9)</p> <p>p&lt;0.001 (95% CI NR)</p> <p><u>Secondary Endpt (TRUNK) # (%):</u></p> <p><i>PGA success</i></p> <p>Trifarotene 255 (42.6)</p> <p>Placebo 182 (29.9)</p>	<p>16.6% /6</p> <p>12.7% /8</p>	<p><u>Severe AE (# of patients):</u></p> <p>T: 3</p> <p>P: 0</p> <p><u>Study w/d due to AE (# of patients):</u></p> <p>T: 1.2%</p> <p>P: 0%</p>	<p><b>Risk of Bias (low/high/unclear):</b></p> <p>See PERFECT 1</p> <p><b>Applicability:</b></p> <p><u>Patient:</u> Patients predominantly white and with skin phototype I or II (of VI), limiting applicability to other skin types (e.g. African-Americans or Latinos).</p> <p><u>Intervention:</u> Intervention appropriate</p> <p><u>Comparator:</u> Placebo appropriate, but comparison with active comparator would enable comparative assessment of clinical efficacy.</p> <p><u>Outcomes:</u> IGA/PGA and lesion count are common outcomes in acne assessment.</p> <p><u>Setting:</u> Over 100 study sites across the United States, Canada, Russia, and Europe; all countries with a predominantly white population.</p>	

after study drug application.  Dosing could be changed by investigator to every other day x 2 weeks, within first 4 weeks from baseline assessment if needed to manage irritation.	Inflammatory: 39.1 ±16.82 Noninflammatory: 45.9 ± 19.87  <u>Key Inclusion Criteria:</u> -identical to PERFECT 1 <u>Key Exclusion Criteria:</u> -identical to PERFECT 1			p<0.001 (95% CI NR)  <i>Inflammatory lesions:</i> Mean absolute Δ from baseline Trifarotene -25.5 (-65.4%) Placebo -19.8 (51.1) p<0.001 (95% CI NR)  <i>Noninflammatory lesions:</i> Mean absolute Δ from baseline Trifarotene -25.9 (-55.2) Placebo -20.8 (45.1%) p<0.001 (95% CI NR)				
<b>Abbreviations:</b> AE = adverse event; ARR = absolute risk reduction; CI = confidence interval; IGA = Investigator’s Global Assessment; ITT = intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PGA = Physician’s Global Assessment; P = placebo vehicle cream group; PP = per protocol; SD = standard deviation; T = trifarotene group; w/d = withdrawal								

## References:

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**Appendix 1: Current Preferred Drug List**

Generic	Brand	Form	Route	PDL
adapalene	ADAPALENE	CREAM (G)	TP	Y
adapalene	DIFFERIN	CREAM (G)	TP	Y
adapalene	ADAPALENE	GEL (GRAM)	TP	Y
adapalene	DIFFERIN	GEL (GRAM)	TP	Y
adapalene	ADAPALENE	GEL W/PUMP	TP	Y
adapalene	DIFFERIN	GEL W/PUMP	TP	Y
adapalene	DIFFERIN	LOTION	TP	Y
adapalene/benzoyl peroxide	ADAPALENE-BENZOYL PEROXIDE	GEL W/PUMP	TP	Y
adapalene/benzoyl peroxide	EPIDUO	GEL W/PUMP	TP	Y
azelaic acid	AZELAIC ACID	GEL (GRAM)	TP	Y
azelaic acid	FINACEA	GEL (GRAM)	TP	Y
benzoyl peroxide	BENZOYL PEROXIDE	CLEANSER	TP	Y
benzoyl peroxide	PACNEX	CLEANSER	TP	Y
benzoyl peroxide	ACNE MEDICATION	GEL (GRAM)	TP	Y
benzoyl peroxide	BENZAC W 10	GEL (GRAM)	TP	Y
benzoyl peroxide	BENZAC W 2.5	GEL (GRAM)	TP	Y
benzoyl peroxide	BENZAC W 5	GEL (GRAM)	TP	Y
benzoyl peroxide	BENZOYL PEROXIDE	GEL (GRAM)	TP	Y
benzoyl peroxide	DEL-AQUA-5	GEL (GRAM)	TP	Y
benzoyl peroxide	PANOXYL AQ 2.5	GEL (GRAM)	TP	Y
benzoyl peroxide	PANOXYL AQ 5	GEL (GRAM)	TP	Y
benzoyl peroxide	BPO	TOWELETTE	TP	Y
clindamycin phos/benzoyl perox	BENZACLIN	GEL (GRAM)	TP	Y
clindamycin phos/benzoyl perox	CLINDAMYCIN PHOS-BENZOYL PEROX	GEL (GRAM)	TP	Y
clindamycin phos/benzoyl perox	CLINDAMYCIN-BENZOYL PEROXIDE	GEL (GRAM)	TP	Y
clindamycin phos/benzoyl perox	DUAC	GEL (GRAM)	TP	Y
clindamycin phos/benzoyl perox	NEUAC	GEL (GRAM)	TP	Y
clindamycin phos/benzoyl perox	ACANYA	GEL W/PUMP	TP	Y
clindamycin phos/benzoyl perox	BENZACLIN	GEL W/PUMP	TP	Y
clindamycin phos/benzoyl perox	CLINDAMYCIN PHOS-BENZOYL PEROX	GEL W/PUMP	TP	Y
clindamycin phos/benzoyl perox	CLINDAMYCIN-BENZOYL PEROXIDE	GEL W/PUMP	TP	Y
clindamycin phosphate	CLINDAMYCIN PHOSPHATE	FOAM	TP	Y
clindamycin phosphate	EVOCLIN	FOAM	TP	Y
clindamycin phosphate	CLEOCIN T	GEL (GRAM)	TP	Y
clindamycin phosphate	CLINDAMYCIN PHOSPHATE	GEL (GRAM)	TP	Y
clindamycin phosphate	CLEOCIN T	LOTION	TP	Y

clindamycin phosphate	CLINDAMYCIN PHOSPHATE	LOTION	TP	Y
clindamycin phosphate	CLEOCIN T	MED. SWAB	TP	Y
clindamycin phosphate	CLINDACIN ETZ	MED. SWAB	TP	Y
clindamycin phosphate	CLINDACIN P	MED. SWAB	TP	Y
clindamycin phosphate	CLINDAMYCIN PHOSPHATE	MED. SWAB	TP	Y
clindamycin phosphate	CLINDAMYCIN PHOSPHATE	SOLUTION	TP	Y
clindamycin/tretinoin	CLINDAMYCIN PHOS-TRETINOIN	GEL (GRAM)	TP	Y
clindamycin/tretinoin	ZIANA	GEL (GRAM)	TP	Y
dapsone	ACZONE	GEL (GRAM)	TP	Y
dapsone	DAPSONE	GEL (GRAM)	TP	Y
erythromycin base in ethanol	ERYGEL	GEL (GRAM)	TP	Y
erythromycin base in ethanol	ERYTHROMYCIN	GEL (GRAM)	TP	Y
erythromycin base in ethanol	ERY	MED. SWAB	TP	Y
erythromycin base in ethanol	ERYTHROMYCIN	MED. SWAB	TP	Y
erythromycin base in ethanol	ERYTHROMYCIN	SOLUTION	TP	Y
isotretinoin	ABSORICA	CAPSULE	PO	Y
isotretinoin	AMNESTEEM	CAPSULE	PO	Y
isotretinoin	CLARAVIS	CAPSULE	PO	Y
isotretinoin	ISOTRETINOIN	CAPSULE	PO	Y
isotretinoin	MYORISAN	CAPSULE	PO	Y
isotretinoin	ZENATANE	CAPSULE	PO	Y
sulfacetamide sodium	KLARON	SUSPENSION	TP	Y
sulfacetamide sodium	SULFACETAMIDE SODIUM	SUSPENSION	TP	Y
tretinoin	AVITA	CREAM (G)	TP	Y
tretinoin	RETIN-A	CREAM (G)	TP	Y
tretinoin	TRETINOIN	CREAM (G)	TP	Y
tretinoin	ATRALIN	GEL (GRAM)	TP	Y
tretinoin	AVITA	GEL (GRAM)	TP	Y
tretinoin	RETIN-A	GEL (GRAM)	TP	Y
tretinoin	TRETINOIN	GEL (GRAM)	TP	Y
tretinoin microspheres	RETIN-A MICRO	GEL (GRAM)	TP	Y
tretinoin microspheres	TRETINOIN MICROSPHERE	GEL (GRAM)	TP	Y
tretinoin microspheres	RETIN-A MICRO PUMP	GEL W/PUMP	TP	Y
tretinoin microspheres	TRETINOIN MICROSPHERE	GEL W/PUMP	TP	Y
adapalene	PLIXDA	MED. SWAB	TP	N
adapalene	ADAPALENE	SOLUTION	TP	N
adapalene/benzoyl peroxide	EPIDUO FORTE	GEL W/PUMP	TP	N
azelaic acid	AZELEX	CREAM (G)	TP	N
azelaic acid	FINEVIN	CREAM (G)	TP	N
azelaic acid	FINACEA	FOAM	TP	N

benzoyl peroxide	PANOXYL	CLEANSER	TP	N
benzoyl peroxide	PANOXYL-4	CLEANSER	TP	N
benzoyl peroxide	BPO	GEL (GRAM)	TP	N
clindamycin phos/benzoyl perox	ONEXTON	GEL (GRAM)	TP	N
clindamycin phos/benzoyl perox	ONEXTON	GEL W/PUMP	TP	N
clindamycin phos/skin clnsr 19	CLINDACIN ETZ	KIT	TP	N
clindamycin phos/skin clnsr 19	CLINDACIN PAC	KIT	TP	N
clindamycin phosphate	CLINDAGEL	GEL DAILY	TP	N
clindamycin phosphate	CLINDAMYCIN PHOSPHATE	GEL DAILY	TP	N
clindamycin/benzoyl/emol cmb94	NEUAC	CMB CR GEL	TP	N
dapsone	ACZONE	GEL W/PUMP	TP	N
erythromycin/benzoyl peroxide	BENZAMYCIN	GEL (GRAM)	TP	N
erythromycin/benzoyl peroxide	ERYTHROMYCIN-BENZOYL PEROXIDE	GEL (GRAM)	TP	N
isotretinoin	ABSORICA	CAPSULE	PO	N
tazarotene	FABIOR	FOAM	TP	N
tretinoin	TRETIN-X	CREAM (G)	TP	N
tretinoin microspheres	RETIN-A MICRO PUMP	GEL W/PUMP	TP	N
tretinoin/emol 9/skin cleansr1	TRETIN-X	COMBO. PKG	TP	N
trifarotene	AKLIEF	CREAM (G)	TP	N
benzoyl peroxide	BENZOYL PEROXIDE	CLEANSER	TP	
benzoyl peroxide	PANOXYL	CLEANSER	TP	
benzoyl peroxide	CLEARASIL DAILY CLEAR	CREAM (G)	TP	
benzoyl peroxide	DEL-AQUA-10	CREAM (G)	TP	
benzoyl peroxide	ACNE MEDICATION	LOTION	TP	
benzoyl peroxide	BENZOYL PEROXIDE	LOTION	TP	
tretinoin	ALTRENO	LOTION	TP	

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## Appendix 2: Abstracts of Comparative Clinical Trials

### **A novel topical minocycline foam for the treatment of moderate-to-severe acne vulgaris: Results of 2 randomized, double-blind, phase 3 studies**

Gold LS, Dhawan S, Weiss J, Draelos ZD, Ellman H, Stuart IA

#### **Background**

FMX101 4% is a topical minocycline foam for the treatment of moderate-to-severe acne.

#### **Objective**

Evaluate the efficacy and safety of FMX101 4% in treating moderate-to-severe acne vulgaris.

#### **Methods**

Two identical phase 3 studies were conducted. Subjects were randomized 2:1 to once-daily FMX101 4% or foam vehicle for 12 weeks. The coprimary end points were the change in inflammatory lesion count from baseline and the rate of treatment success according to the Investigator's Global Assessment (a score of 0 or 1 for clear or almost clear, with a  $\geq 2$ -grade improvement) at week 12.

#### **Results**

A total of 961 subjects were enrolled (study 04, N = 466; study 05, N = 495). Compared with vehicle, FMX101 4% demonstrated a significantly greater reduction in inflammatory lesions in both studies ( $P < .05$ ) and a greater rate of treatment success in study 05 according to the Investigator's Global Assessment ( $P < .05$ ). Pooled analyses of the 2 studies demonstrated statistical significance for both coprimary end points (all  $P < .05$ ). Noninflammatory lesion count was also significantly reduced with FMX101 4% versus with vehicle in both studies. FMX101 4% was generally safe and well tolerated. Skin-related adverse events were reported in less than 1% of subjects treated with FMX101 4%.

#### **Limitations**

Longer-term efficacy and safety outcomes are needed (ongoing).

#### **Conclusion**

FMX101 4% topical minocycline foam significantly reduced both inflammatory and noninflammatory lesions and improved Investigator's Global Assessment scores in patients with moderate-to-severe acne.

J Am Acad Dermatol 2019;80:168-77

<https://doi.org/10.1016/j.jaad.2018.08.020>

### **Novel Tretinoin 0.05% Lotion for the Once-Daily Treatment of Moderate-to-Severe Acne Vulgaris: Assessment of Efficacy and Safety in Patients Aged 9 Years and Older**

Tyring SK, Kircik LH, Pariser DM, Guenin E, Bhatt V, Pillai R

#### **Background**

Topical tretinoin has been extensively studied in clinical trials, and its essential role in the treatment of acne vulgaris (acne) established through evidence-based guidelines.

#### **Objective**

To evaluate efficacy, safety, and tolerability of a novel tretinoin 0.05% lotion in moderate-to-severe acne in patients aged 9 years and older. Methods: A total of 1640 patients, 9-58 years of age were randomized to receive tretinoin 0.05% lotion or vehicle in two double-blind, placebo-controlled 12-week, 2-arm, parallel group studies evaluating safety and efficacy (inflammatory and noninflammatory lesion counts and acne severity using Evaluator Global Severity Scores [EGSS]).

Author: Fletcher

June 2020

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In addition, patients completed a patient satisfaction survey (PSS), Acne-specific quality of life (QoL) questionnaire and assessed their facial skin for shininess/oiliness improvement. The data from these two independent studies were pooled and analyzed.

**Results**

Tretinoin 0.05% lotion demonstrated statistically significant superiority to vehicle in reducing inflammatory and noninflammatory lesion counts (both P less than .001) at week 12 and improving acne severity (P less than .001). At week 12, mean percent change in inflammatory and noninflammatory lesions were 52% and 46%, respectively. Treatment success (a 2-grade improvement in EGSS and 'clear' or 'almost clear' was reported in 18% of patients. Tretinoin 0.05% lotion also showed significantly greater benefits relative to vehicle control in terms of patient satisfaction (P less than .001) and acne-specific QoL domains. Tretinoin 0.05% lotion was very well tolerated with no substantive differences in cutaneous tolerability among treatment groups. No patients discontinued treatment because of adverse events.

**Limitations**

Data from controlled studies may differ from clinical practice.

**Conclusions:**

Tretinoin 0.05% lotion provides statistically significant greater efficacy than vehicle with a highly favorable safety and tolerability profile in moderate-to-severe acne patients.

J Drugs Dermatol. 2018;17(10):1084-1091.

**Appendix 3: Medline Search Strategy**

Step	Search Term	Article #
1	Adapalene/tu, to [Therapeutic Use, Toxicity]	20
2	azelaic acid.mp.	721
3	Benzoyl Peroxide/tu, to [Therapeutic Use, Toxicity]	511
4	Clindamycin/tu, to [Therapeutic Use, Toxicity]	2840
5	Dapsone/tu, th, to [Therapeutic Use, Therapy, Toxicity]	2890
6	Erythromycin/tu, th, to [Therapeutic Use, Therapy, Toxicity]	4499
7	Isotretinoin/tu, to [Therapeutic Use, Toxicity]	1438
8	Sulfacetamide/tu, th, to [Therapeutic Use, Therapy, Toxicity]	109
9	Tretinoin/tu, to [Therapeutic Use, Toxicity]	4089
10	tazarotene.mp.	565
11	trifarotene.mp.	10
12	Contraceptives, Oral/tu, th, to [Therapeutic Use, Therapy, Toxicity]	1542
13	Acne Vulgaris/dt, pc, th [Drug Therapy, Prevention & Control, Therapy]	6727
14	Acne Conglobata/dt, th [Drug Therapy, Therapy]	5
15	acne fulminans.mp.	178
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	18477
17	13 or 14 or 15	6816
18	16 and 17	1792
19	limit 18 to (english language and yr="2018 -Current" and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review"))	28 *24 after duplicates removed

Additional articles found via hand searching of reviews.

## Appendix 4: Prescribing Information Highlights

### HIGHLIGHTS OF PRESCRIBING INFORMATION

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

**AKLIEF® (trifarotene) cream, for topical use**  
**Initial U.S. Approval: 2019**

#### INDICATIONS AND USAGE

AKLIEF Cream is a retinoid indicated for the topical treatment of acne vulgaris in patients 9 years of age and older. (1)

#### DOSAGE AND ADMINISTRATION

- For topical use only. Not for oral, ophthalmic or intravaginal use.
- Apply a thin layer of AKLIEF Cream to the affected areas of the face and/or trunk once a day, in the evening, on clean and dry skin. Avoid contact with the eyes, lips, paranasal creases, and mucous membranes. (2)

#### DOSAGE FORMS AND STRENGTHS

Cream: 0.005% trifarotene. (3)

#### CONTRAINDICATIONS

None (4)

#### WARNINGS AND PRECAUTIONS

- Skin irritation: Erythema, scaling, dryness, and stinging/burning may be experienced with use of AKLIEF Cream. Use a moisturizer from the initiation of treatment, and, if appropriate, reduce the frequency of application of AKLIEF Cream, suspend or discontinue use. (5.1)
- Ultraviolet Light and Environmental Exposure: Minimize exposure to sunlight and sunlamps. Use sunscreen and protective clothing over treated areas when exposure cannot be avoided. (5.2)

#### ADVERSE REACTIONS

Most common adverse reactions (incidence  $\geq 1\%$ ) in patients treated with AKLIEF Cream were application site irritation, application site pruritus, and sunburn (6).

**To report SUSPECTED ADVERSE REACTIONS, contact Galderma Laboratories, L.P. at 1-866-735-4137 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

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

Revised: 10/2019

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**Appendix 5: Key Inclusion Criteria**

<b>Population</b>	Adults and children with acne conglobata, acne fulminans, or severe acne vulgaris
<b>Intervention</b>	Trifarotene topical therapy, other acne therapies (see appendix 3)
<b>Comparator</b>	Placebo or active treatment
<b>Outcomes</b>	Inflammatory and noninflammatory lesion reduction, adverse reactions
<b>Timing</b>	Not applicable
<b>Setting</b>	Outpatient therapy

**Acne Medications**

**Goal(s):**

- Ensure that medications for acne are used appropriately for OHP-funded conditions.

**Length of Authorization:**

- Up to 12 months

**Requires PA:**

- All drugs in the Acne medications class

**Covered Alternatives:**

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for an FDA-approved indication?	<b>Yes:</b> Go to #3	<b>No:</b> Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	<b>Yes:</b> Go to #4	<b>No:</b> Pass to RPh. Deny; not funded by the OHP.
4. Will the prescriber consider a change to a preferred product?  Message: <ul style="list-style-type: none"> <li>• Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy &amp; Therapeutics Committee.</li> </ul>	<b>Yes:</b> Inform prescriber of covered alternatives in class <u>and process appropriate PA.</u>	<b>No:</b> Approve for 12 months.

## Drug Class Update with New Drug Evaluation: Antiepileptics

**Date of Review:** June 2020

**Generic Name:** cenobamate

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

**Purpose for Class Update:** To define place in therapy for a new antiepileptic drug (AED) cenobamate, recently approved by the United States (US) Food and Drug Administration (FDA) for the treatment of focal seizures in adults. In addition, new comparative evidence for antiepileptic agents used in management of seizures will be reviewed.

### Research Questions:

1. Is there new comparative evidence that AEDs differ in efficacy or harms for management of seizures?
2. What is the effectiveness of cenobamate in reducing seizure frequency in adults with focal seizures?
3. What are the comparative harms of cenobamate in adults with focal seizures?
4. Are there certain sub-populations (based on age, gender, ethnicity, comorbidities, disease duration or severity) in which cenobamate may be beneficial or cause more harm?

### Conclusions:

- Nine recently published Cochrane systematic reviews were identified for inclusion in this AED class update.<sup>1-9</sup> Three guidelines were published by the National Institute for Health and Clinical Guidance (NICE)<sup>10-12</sup> and 2 guideline updates were developed by the American Academy of Neurology (AAN) and American Epilepsy Society (AES).<sup>13,14</sup>
- Two Cochrane reviews provided comparative evaluations of oxcarbazepine versus phenytoin<sup>1</sup> and lamotrigine versus carbamazepine<sup>2</sup> when used as monotherapy in patients with epilepsy. Treatment failure due to adverse events occurs significantly later with oxcarbazepine than phenytoin [Hazard Ratio (HR)=0.22, 95% Confidence Interval (CI) 0.10 to 0.51, p=0.0004] based on high-quality evidence.<sup>1</sup> Treatment failure for any reason related to treatment (HR 0.73, 95% CI 0.64 to 0.82, P<0.00001) or due to adverse events (HR 0.54, 95% CI 0.45 to 0.65, P<0.00001) occurs earlier with carbamazepine compared to lamotrigine based on moderate-quality evidence.<sup>2</sup> Neither review demonstrated significant differences in efficacy with one AED compared to another AED.<sup>1,2</sup>
- A Cochrane meta-analysis compared topiramate to placebo as add-on treatment in adults with drug-resistant focal epilepsy.<sup>3</sup> Moderate-quality evidence from 11 trials demonstrated seizure freedom was more likely with topiramate compared to placebo [Relative Risk (RR) 3.67, 95% CI 1.79 to 7.54].<sup>3</sup> The

**Date of Last Review:** January 2019

**Dates of Literature Search:** 08/01/18 – 02/11/20

**Brand Name (Manufacturer):** Xcopri® (SK Life Science, Inc.)

**Dossier Received:** yes

included trials were of relatively short duration and provided no evidence for the long-term efficacy of topiramate.<sup>3</sup> High-quality evidence from 12 studies showed short-term use of add-on topiramate was associated with increased risk of treatment withdrawal due to adverse effects compared with placebo (RR 2.37, 95% CI 1.66 to 3.37).<sup>3</sup>

- A 2019 Cochrane review compared brivaracetam to placebo as add-on therapy for adults with drug-resistant focal epilepsy.<sup>4</sup> Six trials provided data to demonstrate brivaracetam is significantly more effective in reducing seizure frequency compared to placebo (RR 1.81, 95% CI 1.53 to 2.14; moderate-quality evidence).<sup>4</sup> The incidence of treatment withdrawals for any reason was not significantly different between brivaracetam and placebo (RR 1.27, 95% CI 0.94 to 1.76; low-quality evidence).<sup>4</sup> However, the analysis showed that brivaracetam was associated with a significantly higher prevalence of participants withdrawing from treatment, specifically due to adverse events (RR 1.54, 95% CI 1.02 to 2.33; low-quality evidence), compared to those receiving placebo.<sup>4</sup>
- A 2018 Cochrane review evaluated the efficacy and tolerability of gabapentin compared to placebo when used as add-on treatment for people with drug resistant focal epilepsy.<sup>5</sup> Gabapentin was significantly more efficacious than placebo in reducing seizure frequency (RR 1.89, 95% CI 1.40 to 2.55; 6 trials; moderate-quality evidence).<sup>5</sup> Treatment withdrawal with gabapentin was not significantly different compared with placebo (RR 1.05, 95% CI 0.74 to 1.49; moderate-quality evidence).<sup>5</sup> Ataxia, dizziness, fatigue, and somnolence occurred in significantly more gabapentin-treated subjects than placebo.<sup>5</sup> There were no significant differences in headache or nausea between gabapentin and placebo.<sup>5</sup>
- A 2018 Cochrane review compared the efficacy and tolerability of pregabalin with placebo or an alternative AED when used as add-on treatment for individuals with drug-resistant focal epilepsy.<sup>6</sup> Pregabalin was significantly more effective than placebo for reducing seizure frequency by 50% (RR 2.28, 95% CI 1.52 to 3.42, 7 trials, low-quality evidence) and improving seizure freedom (RR 3.94, 95% CI 1.50 to 10.37, 4 trials, moderate-quality evidence).<sup>6</sup> Results demonstrated efficacy for pregabalin doses from 150 mg per day to 600 mg per day, with increasing effectiveness at 600 mg doses; however issues with tolerability were noted at higher doses.<sup>6</sup> Participants were significantly more likely to withdraw from pregabalin treatment than placebo for any reason (RR 1.35, 95% CI 1.11 to 1.65, 7 trials, moderate-quality evidence) and for adverse effects (RR 2.65, 95% CI 1.88 to 3.74, 7 trials, moderate-quality evidence).<sup>6</sup> Compared to pregabalin, no significant differences in reduction of seizure frequency were observed by those allocated to lamotrigine (RR 1.47, 95% CI 1.03 to 2.12, 1 trial), levetiracetam (RR 0.94, 95% CI 0.80 to 1.11, 1 trial) or gabapentin (RR 0.96, 95% CI 0.82 to 1.12, 1 trial).<sup>6</sup> No significant differences were observed between pregabalin and lamotrigine, levetiracetam, or gabapentin for treatment withdrawal due to any reason or due to adverse effects.<sup>6</sup>
- A 2018 Cochrane review evaluated the efficacy and tolerability of rufinamide for people with refractory epilepsy.<sup>7</sup> Rufinamide was significantly more effective than placebo in reducing seizure frequency by at least 50%, when added to conventional AEDs in people with refractory focal epilepsy (RR 1.79, 95% CI 1.44 to 2.22; 6 trials; moderate-quality evidence).<sup>7</sup> Treatment withdrawal (for any reason and due to adverse effects) was significantly more likely with rufinamide than placebo (RR 1.83, 95% CI 1.45 to 2.31; 6 trials; moderate-quality evidence).<sup>7</sup> Adverse effects associated with rufinamide included headache, dizziness, somnolence, vomiting, nausea, fatigue and diplopia.<sup>7</sup>
- A 2019 Cochrane review evaluated clinical trials of pregabalin compared to placebo in treatment of neuropathic pain in adults.<sup>8</sup> Moderate-quality evidence showed pregabalin reduces pain intensity by 50% in post-herpetic neuralgia compared to placebo (pregabalin 32% vs. placebo 13%; RR 2.5, 95% CI 1.9 to 3.4); painful diabetic neuropathy (31% vs. 24%; RR 1.3, 95% CI 1.2 to 1.5); and mixed or unclassified post-traumatic neuropathic pain (34% vs. 20%; RR 1.5 95% CI 1.2 to 1.9), and absence of efficacy in HIV neuropathy.<sup>8</sup> Evidence of pregabalin efficacy in central neuropathic pain is inadequate.<sup>8</sup> When all neuropathic pain studies were analyzed, serious adverse events were no more common with placebo than with pregabalin 300 mg (3.1% vs. 2.6%; RR 1.2, 95% CI 0.8 to 1.7; 17 trials; high-quality evidence) or pregabalin 600 mg (3.4% vs. 3.4%; RR 1.1, 95% CI 0.8 to 1.5; 16 studies; high-quality evidence).<sup>8</sup>
- A 2019 Cochrane review assessed the efficacy and tolerability of valproate for acute manic episodes in bipolar disorder compared to placebo, alternative pharmacological treatments, or combination pharmacological treatments.<sup>9</sup> High-quality evidence shows valproate is an efficacious treatment for acute mania in adults when compared to placebo (45% valproate vs. 29% placebo, Odds Ratio (OR) 2.05, 95% CI 1.32 to 3.20; 4 studies).<sup>9</sup> In contrast, there is no evidence of a difference in efficacy between valproate and placebo for treating acute mania for children and adolescents.<sup>9</sup> Low-quality evidence shows

valproate has little difference in response rate than olanzapine in adults (38% valproate vs. 44%, olanzapine OR 0.77, 95% CI 0.48 to 1.25; 2 studies).<sup>9</sup> Moderate-quality evidence found that more participants receiving valproate experienced adverse events compared to placebo (83% valproate vs. 75% placebo, OR 1.63, 95% CI 1.13 to 2.36; 3 studies).<sup>9</sup> Low-quality evidence found there may be little or no difference in tolerability between valproate and lithium (78% valproate vs. 86%, lithium OR 0.61, 95% CI 0.25 to 1.50; 2 studies).<sup>9</sup>

- In February 2020, NICE strengthened guidance to avoid valproate in women and girls of childbearing potential (including young girls who are likely to need treatment into their childbearing years), unless alternative treatments are not suitable.<sup>10</sup> Women and girls of childbearing potential must be fully informed about the risks of taking valproate during pregnancy, and may only take valproate if they have a pregnancy prevention program in place, in line with the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA) safety advice on valproate.<sup>10</sup> The risk of AEDs causing malformations and possible neurodevelopmental impairments in an unborn child should be discussed with all women of childbearing potential.<sup>10</sup>
- Recommendations for treatment of seizures associated with Dravet syndrome (DS) or Lennox-Gastaut syndrome (LGS) with cannabidiol and clobazam were published by NICE in December 2019.<sup>11,12</sup> Cannabidiol with clobazam is recommended as an option for treating seizures associated with DS or LGS in people aged 2 years and older, with mandatory check of frequency of convulsive seizures every 6 months.<sup>11,12</sup> Cannabidiol should be stopped if seizure frequency has not fallen by at least 30% compared with the 6 months before starting treatment.<sup>11,12</sup>
- In 2018, The AAN and AES published a 2-part guideline update focused on the efficacy and tolerability of recently approved AEDs.<sup>13,14</sup> Part 1 evaluated evidence for treatment of new-onset epilepsy with newer AEDs.<sup>13</sup> In adults with new-onset focal epilepsy, lamotrigine should be considered to decrease seizure frequency.<sup>13</sup> Levetiracetam and zonisamide may be considered as alternatives to decrease seizure frequency in adults with new-onset focal epilepsy.<sup>13</sup> In adults 60 years and older, lamotrigine should be considered in decreasing seizure frequency in patients with new-onset focal epilepsy.<sup>13</sup> Gabapentin may be considered in decreasing seizure frequency in patients with new-onset focal epilepsy.<sup>13</sup> Unless there are compelling adverse effect–related concerns, ethosuximide or valproic acid should be considered before lamotrigine to decrease seizure frequency when treating absence seizures in childhood absence epilepsy.<sup>13</sup>
- Part 2 of the AAN/AES guidance evaluated evidence for treatment-resistant epilepsy with newer AEDs.<sup>14</sup> AED selection depends on seizure/syndrome type, patient age, concomitant medications, and AED tolerability, safety, and efficacy.<sup>14</sup> The following AEDs are established as effective to reduce seizure frequency: immediate-release pregabalin and perampanel for treatment-resistant adult focal epilepsy ; vigabatrin for treatment-resistant adult focal epilepsy (not first-line treatment); and rufinamide for LGS (add-on therapy).<sup>14</sup>

#### *Cenobamate*

- The safety and efficacy of adjunctive oral cenobamate in treating adults with uncontrolled focal seizures was evaluated in a moderate-quality phase 2 randomized controlled trial (RCT).<sup>15</sup> Adult patients with treatment-resistant focal seizures (n=437) taking 1 to 3 AEDs were randomly assigned (1:1:1:1) to once daily oral cenobamate 100 mg, 200 mg, 400 mg, or placebo.<sup>15</sup> The primary outcome was reduction in 28 day focal seizure frequency from baseline to the end of the double-blind treatment phase (12 weeks). Moderate-quality data from this trial demonstrates adjunctive cenobamate significantly reduces focal seizure frequency compared to placebo.<sup>15</sup> Median percentage reductions in seizure frequency over 12 weeks from baseline were 24.0% [Interquartile Range (IQR) 45.0 to 7.0%] for the placebo group compared with 35.5% (IQR 62.5 to 5.0%; p=0.0071 vs. placebo) for the 100 mg dose group, and 55.0% for the 200 mg and 400 mg dose groups (IQR 73.0 to 23.0% and 85.0 to 28.0%, respectively, P<0.0001 vs. placebo for both doses).<sup>15</sup>
- Treatment-emergent adverse events identified in the trial led to discontinuation in 5% of patients in the placebo group, 10% in the 100 mg dose group, 14% in the 200 mg dose group, and 20% in the 400 mg dose group.<sup>15</sup> The most common AEs reported in all the cenobamate trials which occurred in greater than 10% of patients were somnolence, dizziness, fatigue, and diplopia.<sup>16</sup>
- Limitations of this study include the short study duration and the potential effect of concomitant AEDs. In addition, type of seizure and seizure frequency were self-recorded by the subjects, which could contribute to detection bias.<sup>15</sup>

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**Recommendations:**

- Designate cenobamate as non-preferred drug on the Oregon Health Plan (OHP) Practitioner-Managed Prescription Drug Plan (PMPDP).
- Review comparative drug costs in the executive session.

**Summary of Prior Reviews and Current Policy**

Two new AEDs, cannabidiol and stiripentol, were reviewed at the January 2019 Pharmacy and Therapeutics (P and T) Committee meeting. After discussion, the committee recommended the implementation of prior authorization (PA) criteria to ensure medically appropriate utilization of cannabidiol and stiripentol. The preferred oral and rectal AEDs included on the Oregon Medicaid FFS (Fee-For-Service) Preferred Drug List (PDL) are: carbamazepine, diazepam, divalproex, ethosuximide, ethotoin, gabapentin, lacosamide, levetiracetam, methsuximide, oxcarbazepine, phenobarbital, phenytoin, primidone, tiagabine, topiramate, valproic acid, and zonisamide. Lamotrigine is classified as a voluntary medication due to its utilization in mental health treatment. Non-preferred AEDs are listed in **Appendix 1**. The utilization of clobazam, pregabalin, and topiramate is guided by prior authorization (PA) criteria to ensure they are prescribed for indications supported by the medial literature. The PA criteria for cannabidiol, clobazam, pregabalin, stiripentol, and topiramate are presented in **Appendix 4**.

**Medicaid Fee-for-Service Utilization**

A review of pharmacy AED claims paid 7/1/19 through 9/30/19 provided an overview of Medicaid Fee for Service (FFS) utilization in the third quarter of 2019. Ninety-seven percent of the claims were for preferred or voluntary agents in the AED class. The most frequently requested preferred agent was lamotrigine with over 60% of claims, followed by divalproex (20%) and gabapentin (4%). The most requested non-preferred AED was pregabalin followed by clobazam.

**Background:**

In 2014, the International League Against Epilepsy (ILAE) defined epilepsy as a disease of the brain, diagnosis of which requires: (a) at least two unprovoked seizures occurring more than 24 hours apart; (b) one unprovoked seizure with at least 60% probability for further seizures occurring over the next 10 years, or (c) the diagnosis of an epilepsy syndrome.<sup>17</sup> The causes of epilepsy vary and are identified in only about 30% of people with the disorder.<sup>18</sup> Worldwide, an estimated 65 million people have epilepsy.<sup>19</sup> In the United States, approximately 150,000 adults present annually with an unprovoked first seizure.<sup>20</sup> The incidence of epilepsy has a bimodal distribution with the highest risk in infants and older age groups.<sup>21</sup> Common risk factors include premature birth; complicated febrile seizures; infections, such as meningitis or encephalitis; head trauma; or family history of epilepsy or neurologic illnesses.<sup>18</sup> Causes of epilepsy may include structural lesions, abnormalities of neuronal migration, and fetal intracranial hemorrhage.<sup>18</sup> Other acquired lesions can serve as seizure foci, including benign and malignant intracranial or extra-axial tumors, abscesses, cysts, hemorrhagic lesions, or strokes.<sup>18</sup> Systemic illnesses, such as HIV infection and malaria, can also lead to chronic epilepsy.<sup>18</sup>

In 2017, ILAE updated the classification of seizure types based on the initial manifestation of the seizure as generalized, focal, or unknown (if seizure onset is either missed or obscured).<sup>22</sup> Of note, the terms simple partial, complex partial, and secondarily generalized tonic-clonic have been eliminated, since they were difficult to define pragmatically and were often used incorrectly.<sup>22</sup> Generalized seizures are generally distributed bilaterally to both cerebral hemispheres and are further classified as motor (tonic-clonic) or non-motor (absence) seizures.<sup>22</sup> Focal seizures originate within networks limited to one cerebral hemisphere. Focal seizures are further subdivided based on level of patient awareness (aware or impaired awareness).<sup>22</sup> Additionally, focal seizures are subgrouped into motor and non-motor seizures, based on signs and symptoms at onset.<sup>22</sup> Additional descriptors for both generalized and focal seizures may be added based on specific motor or non-motor symptoms.<sup>22</sup>

Antiepileptic drugs work by stabilizing cellular mechanisms that prevent spontaneous neuronal depolarization.<sup>18</sup> The exact mechanisms by which various medications influence this function include interaction through sodium, calcium, or potassium channels or effects on neurotransmitters such as gamma-aminobutyric acid (GABA) or glutamate.<sup>18</sup> Drug selection is based upon seizure type, the adverse effect profile, childbearing potential of the patient, co-prescribed medications, and patient preference. Approximately half of newly diagnosed patients with epilepsy are successfully treated with the first AED; however, treatment failure and drug intolerance can occur. Monotherapy is more likely to promote compliance, reduce potential for drug interactions, and is less costly but may not keep a patient seizure-free. For approximately 70% of people with epilepsy, seizures can be controlled with a single antiepileptic drug.<sup>23</sup> The remaining 30% of individuals experience refractory or drug-resistant seizures, which often require combinations of AEDs or alternative treatments such as surgery.<sup>24</sup> According to a 2010 ILAE task force, drug-resistant epilepsy may be defined as “failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom”.<sup>25</sup>

The pharmacologic management of patients with epilepsy is focused on 3 main goals: 1) controlling seizures, 2) avoiding adverse effects, and 3) maintaining or restoring quality of life.<sup>26</sup> The NICE epilepsy guidelines provide detailed prescribing considerations for AEDs.<sup>27</sup> According to the 2012 NICE guidelines, first-line agents for treatment of focal seizures include carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, and valproate.<sup>27</sup> Second-line agents include clobazam, gabapentin, and topiramate.<sup>27</sup> For generalized motor seizures first-line options include valproate, lamotrigine, carbamazepine, or oxcarbazepine.<sup>27</sup> Clobazam, levetiracetam, or topiramate are second-line agents if first-line agents are ineffective or not tolerated.<sup>27</sup> If non-motor seizures are present, then carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin are not recommended as they can precipitate or aggravate seizures.<sup>27</sup> Per the 2012 NICE guidance, ethosuximide, valproate, and lamotrigine are the recommended agents to treat absence seizures.<sup>27</sup> Most of the newer AEDs have been developed in an effort to improve safety and tolerability.

Indications for immediate AED treatment are based largely on estimations of an individual's risk of a seizure recurrence.<sup>28</sup> Evidence indicates that immediate AED therapy is likely to reduce seizure recurrence risk for individuals with an unprovoked first seizure, particularly within the first 2 years.<sup>28</sup> Such seizure recurrence prevention, even in the short term, may be important, with potentially greater implications for adults than for children.<sup>28</sup> For adults, seizure recurrences may cause such serious psychological and social consequences as loss of driving privileges and limitations on employment.<sup>28</sup> Although individual seizure recurrences pose some risk for physical harm and even death, there is no evidence that immediate AED treatment reduces that risk or improves quality of life (QOL).<sup>28</sup> The issue of exactly how to use complicated risk data of recurrences and seizure remission to guide management is a question that warrants further research and clarification.<sup>28</sup>

#### **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:**

### *Cochrane Meta-Analyses of Individual Participant Data*

A series of Cochrane reviews evaluating pair-wise monotherapy comparisons of carbamazepine, lamotrigine, topiramate, oxcarbazepine, phenobarbital, phenytoin and valproate in treating epilepsy were updated in 2018 and 2019.<sup>1,2,29-33</sup> Each of these updates compiled a meta-analysis of individual participant data (IPD), in which the raw individual level data for each study were obtained from the investigators and used for synthesis of the meta-analysis.<sup>34</sup> Traditional meta-analysis methods involve combining quantitative evidence from related studies to evaluate outcomes. The goal of IPD meta-analysis is to summarize the raw data on a specific clinical question from multiple related studies.<sup>34</sup> IPD analyses are time consuming to generate because the original investigators must be contacted to ask if they will share their raw data for the report. Only the updates that were based on moderate to high quality evidence will be described in detail for this class update. Five separate updates evaluated carbamazepine with phenobarbital,<sup>29</sup> carbamazepine with phenytoin,<sup>30</sup> phenytoin with valproate,<sup>31</sup> topiramate with carbamazepine,<sup>32</sup> and phenobarbital with phenytoin,<sup>33</sup> but the recently published trials included in these updates were imprecise and may have misclassified seizure type, so the methodological quality of the evidence was rated as low by the Cochrane reviewers. Therefore, they are not included in this summary. Two IPD meta-analyses based on moderate quality evidence are summarized below.

#### *Oxcarbazepine versus Phenytoin*

A 2018 Cochrane review updated a previous 2013 publication comparing oxcarbazepine to phenytoin monotherapy in people with focal onset seizures or generalized motor seizures using the IPD methodology.<sup>1</sup> Literature was searched through August 2018. Evidence from 3 studies (n=517) met inclusion criteria.<sup>1</sup> The results of this review are applicable mainly to individuals with focal onset seizures; 70% of included individuals experienced seizures of this type at baseline.<sup>1</sup> The primary outcome was time to treatment failure (retention time). Secondary outcomes included remission, time to first seizure with oxcarbazepine compared to phenytoin, and incidence of adverse events. The 2 studies included in IPD meta-analysis were generally of good methodological quality but the design of the studies may have biased the results for some of the secondary outcomes (time to first seizure post-randomization, time to six-month and 12-month remission) as seizure recurrence data were not collected following treatment failure or withdrawal from the study.<sup>1</sup>

Data from 2 trials (n=480) were combined to assess time to treatment failure. For this outcome, a HR less than one indicates a clinical advantage for oxcarbazepine.<sup>1</sup> Time to treatment failure for any reason related to treatment was not statistically significant when oxcarbazepine was compared to phenytoin (pooled HR 0.78, 95% CI 0.53 to 1.14, P=0.20, moderate-quality evidence).<sup>1</sup> Treatment failure due to adverse events occurred later with oxcarbazepine than phenytoin (HR=0.22, 95% CI 0.10 to 0.51, p=0.0004, high-quality evidence).<sup>1</sup> Time to treatment failure due to lack of efficacy showed no clear difference between oxcarbazepine and phenytoin (HR=1.17, 95% CI 0.31 to 4.35, p=0.82, moderate-quality evidence).<sup>1</sup> The most common adverse events reported in more than 10% of participants on either drug were somnolence (28% of total participants, with similar rates for both drugs), headache (15% of total participants, with similar rates for both drugs), dizziness [14.5% of total participants, reported by more participants on phenytoin (18%) than oxcarbazepine (11%)] and gum hyperplasia [reported by substantially more participants on phenytoin (18%) than oxcarbazepine (2%)]; confidence intervals and statistical significance were not provided for adverse event rates.<sup>1</sup> In summary, high-quality evidence provided by this review indicates that treatment failure due to adverse events occurs significantly later with oxcarbazepine than phenytoin.<sup>1</sup>

#### *Lamotrigine versus Carbamazepine*

A 2018 Cochrane review updated a previous 2006 publication comparing lamotrigine to carbamazepine monotherapy in people with focal onset seizures or generalized motor seizures using the IPD methodology.<sup>2</sup> Literature was searched through February 2018. Fourteen trials met inclusion criteria. Individual participant data were available for 2572 participants out of 3787 eligible individuals from 9 out of 14 trials.<sup>2</sup> For remission outcomes, a HR of less than one indicated an advantage for carbamazepine; and for first seizure and treatment failure outcomes, a HR of less than one indicated an advantage for lamotrigine.<sup>2</sup>

Of 3768 participants that had reasons for treatment failure or withdrawal, 38% of all participants prematurely withdrew from treatment (33% of participants randomized to lamotrigine and 44% participants randomized to carbamazepine).<sup>2</sup> Eighty-six percent of total treatment failures were in subjects who withdrew for reasons related to the allocated drug: 86% of treatment failures for lamotrigine and 87% of treatment failures for carbamazepine.<sup>2</sup> The most common treatment-related reason for treatment failure was adverse events noted in 44% of total treatment failures. Thirty-six percent of total treatment failures were for lamotrigine and 52% of total treatment failures for carbamazepine.<sup>2</sup> Time to treatment failure for any reason was HR 0.73 (95% CI 0.64 to 0.82,  $P < 0.00001$ ,  $I^2 = 13\%$  moderate-quality evidence,  $n = 2569$ , 9 trials) indicating a statistically significant advantage with lamotrigine versus carbamazepine.<sup>2</sup> For time to treatment failure due to adverse events, the overall pooled HR was 0.54 (95% CI 0.45 to 0.65,  $P < 0.00001$ , moderate-quality evidence) indicating a statistically significant advantage with lamotrigine.<sup>2</sup> Considering time to treatment failure due to lack of efficacy, 1874 participants provided IPD from 5 trials; no participants withdrew from one or both of the drugs due to lack of efficacy in four trials.<sup>2</sup> The overall pooled HR was 1.03 (95% CI 0.75 to 1.41,  $P = 0.86$ ,  $I^2 = 0\%$  moderate-quality evidence) indicating no statistically significant difference between lamotrigine and carbamazepine.<sup>2</sup> In summary, moderate quality evidence indicates that treatment failure for any reason related to treatment or due to adverse events occurs significantly earlier with carbamazepine compared to lamotrigine.<sup>2</sup>

#### Cochrane: Topiramate Add-On Therapy for Drug-Resistant Epilepsy

A 2019 Cochrane review updated a previous review focused on topiramate efficacy and tolerability as add-on therapy for people with drug-resistant focal epilepsy.<sup>3</sup> The literature search was completed through July 2018. Twelve trials ( $n = 1650$ ) met inclusion criteria. Topiramate doses ranged from 200 mg per day to 1000 mg per day.<sup>3</sup> The primary outcome was the proportion of people with a 50% or greater reduction in seizure frequency compared to baseline.<sup>3</sup> Secondary outcomes included the proportion of people with complete seizure cessation and treatment withdrawal for any reason.<sup>3</sup> Ten RCTs compared topiramate to placebo in adults (aged 18 to 75 years), one RCT compared topiramate to placebo in children (aged 1 to 16 years), and one RCT compared topiramate to placebo in elderly patients (aged over 65 years). In all trials, participants were eligible if they experienced a minimum number of focal seizures (range 3 to 12 seizures) and were currently taking more than one AED.<sup>3</sup> Treatment periods ranged from 11 to 19 weeks. Eleven studies included in the meta-analysis were rated as having low risk of bias.<sup>3</sup> The RCT conducted in elderly patients had an unclear risk of bias due to insufficient descriptions of allocation concealment, blinding of investigators, and blinding for outcome assessment.<sup>3</sup>

Response to therapy (50% or greater reduction in seizure frequency) was more likely with topiramate compared to placebo (RR 4.36, 95% CI 2.24 to 8.50; 11 studies,  $I^2 = 0$ ; high-certainty evidence).<sup>3</sup> Seizure freedom was also more likely with topiramate compared to placebo (RR 3.67, 95% CI 1.79 to 7.54; 8 studies; moderate-certainty evidence).<sup>3</sup> However, participants were more likely to withdraw from the study early when assigned to topiramate than placebo (RR 2.37, 95% CI 1.66 to 3.37; 12 studies; high-certainty evidence).<sup>3</sup> Specifically, add-on topiramate was associated with a higher incidence of the following adverse effects compared to placebo: ataxia (RR 2.29, 95% CI 1.10 to 4.77,  $P = 0.003$ ), concentration difficulties (RR 7.81, 95% CI 2.08 to 29.29,  $P < 0.001$ ), dizziness (RR 1.52, 95% CI 1.07 to 2.16,  $P = 0.002$ ), fatigue (RR 2.08, 95% CI 1.37 to 3.15,  $P < 0.001$ ), paresthesia (RR 3.65, 95% CI 1.58 to 8.39,  $P < 0.001$ ), somnolence (RR 2.44, 95% CI 1.61 to 3.68,  $P < 0.001$ ), speech difficulty (RR 3.37, 95% CI 0.80 to 14.13,  $P = 0.03$ ), and weight loss (RR 3.99, 95% CI 1.82 to 8.72,  $P < 0.001$ ).<sup>3</sup>

In summary, topiramate is efficacious as add-on treatment for drug-resistant focal epilepsy as it is more effective than placebo at reducing seizure frequency in adults.<sup>3</sup> However, the trials reviewed were of relatively short duration and provided no evidence for the long-term efficacy.<sup>3</sup> Short-term use of add-on topiramate was shown to be associated with increased risk of adverse events compared with placebo.<sup>3</sup>

### Cochrane: Brivaracetam Add-On Therapy for Drug-Resistant Epilepsy

A 2019 Cochrane review evaluated the efficacy and tolerability of brivaracetam when used as add-on treatment for people with drug-resistant epilepsy.<sup>35</sup> The literature search was conducted through October 2018. Six double-blind, placebo-controlled RCTs representing 2411 participants met inclusion criteria.<sup>35</sup> One study included participants with both focal and generalized onset seizures; the other 5 trials included participants with focal onset seizures only.<sup>35</sup> All 6 studies included adult participants between 16 and 80 years of age, and treatment periods ranged from 7 to 16 weeks.<sup>35</sup> Two studies were judged to have low risk of bias and 4 studies had unclear risk of bias.<sup>35</sup> One study failed to provide details on the method used for allocation concealment, and one did not report all outcomes prespecified in the trial protocol.<sup>35</sup> One study did not describe how blinding was maintained, and another noted discrepancies in reporting.<sup>35</sup> The primary outcome was the proportion of individuals with a 50% or greater reduction in seizure frequency compared to baseline.<sup>35</sup> Secondary outcomes included proportion of patients with complete seizure cessation, treatment withdrawal, and adverse effects.

Participants who received brivaracetam were more likely to achieve a 50% or greater reduction in seizure frequency, compared to those who received placebo (RR 1.81, 95% CI 1.53 to 2.14,  $I^2$  not reported, moderate-quality evidence).<sup>35</sup> Participants who received brivaracetam were more likely to experience seizure freedom than those on placebo (RR 5.89, 95% CI 2.30 to 15.13;  $I^2=0%$ , moderate-quality evidence).<sup>35</sup> No difference was found in the proportion of participants who withdrew from treatment between those assigned to brivaracetam versus placebo (RR 1.27, 95% CI 0.94 to 1.74,  $I^2$  not reported, low-quality evidence).<sup>35</sup> In contrast, those who received brivaracetam were more likely to withdraw from treatment due to adverse events (RR 1.54, 95% CI 1.02 to 2.33; low-quality evidence), compared to placebo.<sup>35</sup>

In summary, brivaracetam, when used as add-on therapy for adults patients with drug-resistant focal epilepsy, is effective in reducing seizure frequency compared to placebo.<sup>35</sup> The incidence of treatment withdrawals for any reason was not significantly different between brivaracetam and placebo.<sup>35</sup> However, add-on brivaracetam was associated with a greater proportion of treatment withdrawals due to adverse events compared with placebo.<sup>35</sup> None of the studies included participants under the age of 16, and all studies were of short duration.<sup>35</sup>

### Gabapentin Add-on Therapy for Drug-Resistant Focal Epilepsy

A 2018 Cochrane review updated a previously published 2013 version to evaluate the efficacy and tolerability of gabapentin when used as add-on treatment for people with drug resistant focal epilepsy.<sup>5</sup> The literature search was conducted through March 2018. Data from 6 trials were included in the meta-analyses of 1206 randomized participants.<sup>5</sup> Overall, the studies were rated at low to unclear risk of bias due to incomplete information. The overall quality of evidence was judged as low to moderate due to potential attrition bias resulting from missing outcome data and imprecise results with wide confidence intervals.<sup>5</sup>

Reduction in seizure frequency was more likely with gabapentin compared to placebo (RR 1.89, 95% CI 1.40 to 2.55; 6 trials, 1206 participants; moderate-quality evidence).<sup>5</sup> No significant differences in proportion of patients withdrawing from treatment between gabapentin and placebo were observed (RR 1.05, 95% CI 0.74 to 1.49; moderate-quality evidence).<sup>5</sup> Adverse effects higher with gabapentin than placebo for the following: ataxia 2.01 (99% CI 0.98 to 4.11; 3 studies, 787 participants; low-quality evidence), dizziness 2.43 (99% CI 1.44 to 4.12; 6 studies, 1206 participants; moderate-quality evidence), fatigue 1.95 (99% CI 0.99 to 3.82; 5 studies, 1161 participants; low-quality evidence) and somnolence 1.93 (99% CI 1.22 to 3.06; 6 studies, 1206 participants; moderate-quality evidence).<sup>5</sup> No differences were noted between gabapentin and placebo for headache (RR 0.79, 99% CI 0.46 to 1.35; 6 studies, 1206 participants; moderate-quality evidence) or nausea (RR 0.95, 99% CI 0.52 to 1.73; 4 trials, 1034 participants; moderate-quality evidence).<sup>5</sup>

In summary, gabapentin efficacious compared to placebo when studied as an add-on treatment in patients with drug-resistant focal epilepsy.<sup>5</sup> However, the trials reviewed were of relatively short duration and provide no evidence for the long-term efficacy of gabapentin beyond 3 months.<sup>5</sup> The results cannot be extrapolated to monotherapy or to people with other epilepsy types.<sup>5</sup>

#### Cochrane: Pregabalin Add-on Therapy for Drug-Resistant Focal Epilepsy

A 2018 Cochrane review updated a previously published 2014 version to evaluate the efficacy and tolerability of pregabalin when used as add-on treatment for individuals with drug resistant focal epilepsy.<sup>6</sup> Literature was searched through July 2018. Nine industry-sponsored randomized controlled trials (3327 participants) are included in the update.<sup>6</sup> Three RCTs were recently identified and analyzed with the additional 6 RCTs identified in the 2014 review.<sup>6</sup>

For the primary outcome, participants randomized to pregabalin were more likely to attain a 50% or greater reduction in seizure frequency compared to placebo (RR 2.28, 95% CI 1.52 to 3.42, 7 trials, 2193 participants, low-quality evidence).<sup>6</sup> The odds of response doubled with an increase in pregabalin dose from 300 mg per day to 600 mg per day (OR 1.99, 95% CI 1.74 to 2.28), indicating a dose-response relationship.<sup>6</sup> More patients were seizure-free on pregabalin compared to placebo (RR 3.94, 95% CI 1.50 to 10.37, 4 trials, 1125 participants, moderate-quality evidence).<sup>6</sup> However, patients were more likely to withdraw from pregabalin treatment than placebo for any reason (RR 1.35, 95% CI 1.11 to 1.65, 7 trials, 2193 participants, moderate-quality evidence) and for adverse effects (RR 2.65, 95% CI 1.88 to 3.74, 7 trials, 2193 participants, moderate-quality evidence).<sup>6</sup> Analyses pooling across doses (50 mg per day to 600 mg per day immediate- and controlled-release pregabalin) indicated that ataxia (RR 3.90, 99% CI 2.05 to 7.42); dizziness (RR 3.15, 99% CI 2.23 to 4.44); fatigue (RR 1.34, 99% CI 0.93 to 1.94); somnolence (RR 2.15, 99% CI 1.50 to 3.09); and weight gain (RR 5.02, 99% CI 2.49 to 10.10) were all more prevalent in participants randomized to pregabalin compared to placebo.<sup>6</sup> Incidence of nausea did not differ between pregabalin and placebo groups (RR 1.20, 99% CI 0.56 to 2.58).<sup>6</sup> In contrast, participants randomized to pregabalin were less likely to experience headache compared to those randomized to placebo (RR 0.63, 99% CI 0.42 to 0.93).<sup>6</sup>

Three trials compared pregabalin to active-control drugs: lamotrigine, levetiracetam, and gabapentin.<sup>6</sup> Compared to pregabalin, no differences in reduction of seizure frequency were observed with those allocated to lamotrigine (RR 1.47, 95% CI 1.03 to 2.12, 1 trial, 293 participants), levetiracetam (RR 0.94, 95% CI 0.80 to 1.11, 1 trial, 509 participants) or gabapentin (RR 0.96, 95% CI 0.82 to 1.12, 1 trial, 484 participants).<sup>6</sup> No differences were observed between pregabalin and lamotrigine (RR 1.07, 95% CI 0.75 to 1.52), levetiracetam (RR 1.03, 95% CI 0.71 to 1.49), or gabapentin (RR 0.78, 95% CI 0.57 to 1.07) for treatment withdrawal due to any reason or due to adverse effects (pregabalin vs. lamotrigine: RR 0.89, 95% CI 0.53 to 1.48; vs. levetiracetam: RR 1.29, 95% CI 0.66 to 2.54; vs. gabapentin: RR 1.07, 95% CI 0.54 to 2.11).<sup>6</sup>

Pregabalin, when used as an add-on drug for treatment-resistant focal epilepsy, is more effective than placebo at producing a 50% or greater seizure reduction and seizure freedom. Results demonstrated efficacy for doses from 150 to 600 mg per day, with increasing effectiveness at 600 mg per day; however, issues with tolerability were noted at higher doses.<sup>6</sup> The evidence suggests that there is no significant difference in efficacy and harms between pregabalin and some of the other AEDs gabapentin, levetiracetam, and lamotrigine.<sup>6</sup> The trials included in this review were of short duration.<sup>6</sup>

#### Cochrane: Rufinamide Add-on Therapy for Refractory Epilepsy

A 2018 Cochrane review evaluated the efficacy and tolerability of add-on rufinamide for people with refractory epilepsy.<sup>7</sup> The literature search was conducted through October 2017. The review included 6 trials, representing 1759 participants.<sup>7</sup> Four trials (1563 participants) included people with uncontrolled focal seizures. Two trials (196 participants) included patients with LGS. Overall, the age of the adults ranged from 18 to 80 years and the age of the infants ranged from 4 to 16 years.<sup>7</sup> Baseline phase ranged from 28 to 56 days and double-blind phases from 84 to 96 days.<sup>7</sup> Five of the 6 included trials described adequate

methods of concealment of randomization and only 3 trials adequately described blinding.<sup>7</sup> Overall, the evidence was assessed as moderate to low quality, due to potential risk of bias from some studies contributing to the analysis and wide CIs.

Rufinamide added to current AED treatment was more effective than placebo added to current AED in reducing seizure frequency by at least 50%, when used in people with refractory focal epilepsy (RR 1.79, 95% CI 1.44 to 2.22; 6 RCTs; moderate-quality evidence).<sup>7</sup> Treatment withdrawal (for any reason and due to adverse effects) was more likely with the rufinamide group than placebo (RR 1.83, 95% CI 1.45 to 2.31; 6 RCTs; moderate-quality evidence).<sup>7</sup> Adverse events associated with rufinamide included: headache 1.36 (95% CI 1.08 to 1.69; 3 RCTs; high-quality evidence); dizziness 2.52 (95% CI 1.90 to 3.34; 3 RCTs; moderate-quality evidence); somnolence 1.94 (95% CI 1.44 to 2.61; 6 RCTs; moderate-quality evidence); vomiting 2.95 (95% CI 1.80 to 4.82; 4 RCTs; low-quality evidence); nausea 1.87 (95% CI 1.33 to 2.64; 3 RCTs; moderate-quality evidence); fatigue 1.46 (95% CI 1.08 to 1.97; 3 RCTs; moderate-quality evidence); and diplopia 4.60 (95% CI 2.53 to 8.38; 3 RCTs; low-quality evidence).<sup>7</sup> There was no important heterogeneity between studies for any of the outcomes.

In people with drug-resistant focal epilepsy, rufinamide when used as an add-on treatment was effective in reducing seizure frequency but with several adverse effects.<sup>7</sup> The trials reviewed were of relatively short duration and provided no evidence for the long-term use of rufinamide.<sup>7</sup>

#### Cochrane: Pregabalin for Neuropathic Pain

A 2019 Cochrane review updated a previous 2009 Cochrane publication focused on pregabalin for acute and chronic pain in adults.<sup>8</sup> For this update, the literature search was narrowed to evaluate clinical trials that used pregabalin to treat neuropathic pain in adults.<sup>8</sup> Literature was searched through August 2018. Thirty-one new studies with 8045 participants were identified.<sup>8</sup> Studies lasted 2 to 16 weeks. A diagnosis of post-herpetic neuralgia, painful diabetic neuropathy, or mixed neuropathic pain were the most frequent indications (85% of participants).<sup>8</sup>

#### *Post-Herpetic Neuralgia*

In subjects with post-herpetic neuralgia, more participants had at least 30% pain intensity reduction with pregabalin 300 mg than with placebo [50% vs. 25%; RR 2.1 (95% CI 1.6 to 2.6); NNT 4 (95% CI 3.0 to 5.6); 3 studies, 589 participants, moderate-quality evidence], and more subjects had at least 50% pain intensity reduction [32% vs 13%; RR 2.5 (95% CI 1.9 to 3.4); NNT 6 (95% CI 3.9 to 8.1); 4 studies, 713 participants, moderate-quality evidence].<sup>8</sup> More participants had at least 30% pain intensity reduction with pregabalin 600 mg than with placebo [62% vs. 24%; RR 2.5 (95% CI 2.0 to 3.2); NNT 3 (95% CI 2.2 to 3.7); 3 studies, 537 participants, moderate-quality evidence], and more had at least 50% pain intensity reduction [41% vs. 15%; RR 2.7 (95% CI 2.0 to 3.5); NNT 4 (95% CI 3.1 to 5.5); 4 studies, 732 participants, moderate-quality evidence].<sup>8</sup> Somnolence and dizziness were more common with pregabalin than with placebo based on moderate-quality evidence (somnolence: 300 mg 16% vs. 5.5% and 600 mg 25% vs. 5.8%; dizziness: 300 mg 29% vs. 8.1% and 600 mg 35% vs. 8.8%, respectively).<sup>8</sup>

#### *Painful Diabetic Neuropathy*

In patients with diabetic neuropathy, more participants had at least 30% pain intensity reduction with pregabalin 300 mg than with placebo [47% vs. 42%; RR 1.1 (95% CI 1.01 to 1.2); NNT 22 (95% CI 12 to 200); 8 studies, 2320 participants, moderate-quality evidence], more had at least 50% pain intensity reduction [31% vs. 24%; RR 1.3 (95% CI 1.2 to 1.5); NNT 22 (95% CI 12 to 200); 11 studies, 2931 participants, moderate-quality evidence].<sup>8</sup> More participants had at least 30% pain intensity reduction with pregabalin 600 mg than with placebo [63% vs. 52%; RR 1.2 (95% CI 1.04 to 1.4); NNT 10 (95% CI 5.5 to 41); 2 studies, 611 participants, low-quality evidence], and more had at least 50% pain intensity reduction [41% vs. 28%; RR 1.4 (95% CI 1.2 to 1.7); NNT 8 (95% CI 5.4 to 14); 5 studies, 1015 participants, low-quality evidence].<sup>8</sup> Somnolence and dizziness were more common with pregabalin than with placebo based on moderate-quality evidence (somnolence: 300 mg 11% vs. 3.1% and 600 mg 15% vs. 4.5%; dizziness: 300 mg 13% vs. 3.8% and 600 mg 22% vs. 4.4%).<sup>8</sup>

### *Mixed or Unclassified Post-Traumatic Neuropathic Pain*

For mixed or unclassified post-traumatic neuropathic pain, more participants had at least 30% pain intensity reduction with pregabalin 600 mg than with placebo [48% vs. 36%; RR 1.2 (1.1 to 1.4); NNT 9 (95% CI 5.7 to 15); 4 studies, 1367 participants, low-quality evidence], and more had at least 50% pain intensity reduction [34% vs. 20%; RR 1.5 (95% CI 1.2 to 1.9); NNT 8 (95% CI 5.4 to 11); 4 studies, 1367 participants, moderate-quality evidence].<sup>8</sup> Somnolence (12% vs. 3.9%) and dizziness (23% vs. 6.2%) were more common with pregabalin.<sup>8</sup>

### *Central Neuropathic Pain*

In subjects with central neuropathic pain, more participants had at least 30% pain intensity reduction with pregabalin 600 mg than with placebo [44% vs. 28%; RR 1.6 (95% CI 1.3 to 2.0); NNT 6 (95% CI 4.1 to 11); 3 studies, 562 participants, low-quality evidence] and at least 50% pain intensity reduction [26% vs. 15%; RR 1.7 (95% CI 1.2 to 2.3); NNT 10 (95% CI 6.0 to 28); 3 studies, 562 participants, low-quality evidence].<sup>8</sup> Somnolence (32% vs. 11%) and dizziness (23% vs. 8.6%) were more common with pregabalin than placebo, respectively.<sup>8</sup>

### *Other Neuropathic Pain Conditions*

Studies show no evidence of benefit for 600 mg pregabalin in HIV neuropathy (2 studies, 674 participants, moderate-quality evidence) and limited evidence of benefit in neuropathic back pain or sciatica, neuropathic cancer pain, or polyneuropathy.<sup>8</sup>

In summary, moderate quality evidence demonstrated efficacy with pregabalin at reducing pain intensity by 50% in post-herpetic neuralgia, painful diabetic neuropathy, and mixed or unclassified post-traumatic neuropathic pain, and absence of efficacy in HIV neuropathy. Evidence of efficacy in central neuropathic pain was inadequate.<sup>8</sup> When all neuropathic pain studies were analyzed in a meta-analysis, serious adverse events were no more common with placebo than with pregabalin 300 mg (3.1% vs. 2.6%; RR 1.2, 95% CI 0.8 to 1.7; 17 studies, 4112 participants, high-quality evidence) or pregabalin 600 mg (3.4% vs. 3.4%; RR 1.1, 95% CI 0.8 to 1.5; 16 studies, 3995 participants, high-quality evidence).<sup>8</sup>

### *Cochrane: Valproate for Acute Mania*

A 2019 Cochrane review assessed the efficacy and tolerability of valproate for acute manic episodes in bipolar disorder compared to placebo or alternative pharmacological treatments in pediatric, adolescent and adult populations.<sup>9</sup> Twenty-five trials (3252 participants) compared valproate with either placebo or alternative anti-manic treatments (lithium, olanzapine, risperidone) to alleviate the symptoms of acute mania.<sup>9</sup> The primary outcome to assess efficacy was response rate.<sup>9</sup> The primary outcome to assess tolerability was the number of participants with any adverse effect.<sup>9</sup> The majority of studies focused on adult men and women (aged 18 and above), were conducted in inpatient settings and completed in the US.<sup>9</sup> Five studies in this review focused on children and adolescents (aged 18 and under), expanding the age range of the review from 3 to 82 years.<sup>9</sup> Nine studies included data collected outside the US, namely Iran (4 studies), India (3 studies), China (1 study), or across several countries (1 study).<sup>9</sup>

Valproate induced a slightly higher response in alleviating manic symptoms in adults compared to placebo (45% vs. 29%, OR 2.05, 95% CI 1.32 to 3.20; 4 studies, 869 participants) based on high quality evidence.<sup>9</sup> No difference in response rates were found between valproate and lithium (56% vs. 62%, OR 0.80, 95% CI 0.48 to 1.35; 3 studies, 356 participants) based on moderate-quality evidence.<sup>9</sup> In addition no difference in response rate was found between valproate and olanzapine (38% vs. 44%, OR 0.77, 95% CI 0.48 to 1.25; 2 studies, 667 participants) based on low-quality evidence.<sup>9</sup>

In the children and adolescent population, differences in response rates between valproate and placebo was uncertain (23% vs. 22%, OR 1.11, 95% CI 0.51 to 2.38; 1 study, 151 participants, low-quality evidence).<sup>9</sup> Response rates of patients who received valproate were lower compared to risperidone (23% vs. 66%, OR

0.16, 95% CI 0.08 to 0.29; 1 study, 197 participants) based on low-quality evidence.<sup>9</sup> The evidence regarding any difference in response rates between valproate and lithium was uncertain (23% vs. 34%, OR 0.57, 95% CI 0.31 to 1.07; 1 study, 197 participants, low-quality evidence).<sup>9</sup>

More participants who received valproate experienced an adverse event compared to placebo (83% vs. 75%, OR 1.63, 95% CI 1.13 to 2.36; 3 studies, 745 participants) based on moderate-quality evidence.<sup>9</sup> No difference in tolerability between valproate and lithium was found (78% vs. 86%, OR 0.61, 95% CI 0.25 to 1.50; 2 studies, 164 participants) based on low-quality evidence.<sup>9</sup> Primary tolerability outcome data on the olanzapine comparison with valproate were not obtained.<sup>9</sup> Within the children and adolescent population, the evidence regarding any difference between valproate or placebo was uncertain (67% vs. 60%, OR 1.39, 95% CI 0.71 to 2.71; 1 study, 150 participants, very low-quality evidence).<sup>9</sup> Primary tolerability outcome data on the lithium or risperidone comparisons with valproate were not obtained.<sup>9</sup>

In summary, there is evidence that valproate is an efficacious treatment for acute mania in adults when compared to placebo.<sup>9</sup> By contrast, there is no evidence of a difference in efficacy between valproate and placebo for children and adolescents.<sup>9</sup> Valproate may be less efficacious than olanzapine in adults, and may also be inferior to risperidone as a monotherapy treatment for pediatric mania.<sup>9</sup>

#### *Excluded Systematic Reviews*

After review, 13 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses)<sup>36-39</sup>, wrong study design of included trials (e.g., observational)<sup>40-47</sup>, comparator (e.g., no control or placebo-controlled)<sup>48,49</sup>, or outcome studied (e.g., non-clinical)<sup>50</sup>.

## **NEW GUIDELINES**

### NATIONAL INSTITUTE OF HEALTH AND CARE EXCELLENCE

#### *Epilepsy Diagnosis and Management*

In February 2020 NICE strengthened guidance that valproate must not be used in women and girls of childbearing potential (including young girls who are likely to need treatment into their childbearing years), unless alternative treatments are not suitable.<sup>10</sup> Women and girls of childbearing potential must be fully informed about the risks of taking valproate during pregnancy, and only take valproate if they have a pregnancy prevention program in place, in line with the UK MHRA safety advice on valproate.<sup>51</sup> The risk of AEDs causing malformations and possible neurodevelopmental impairments in an unborn child should be discussed with all women of childbearing potential.<sup>10</sup> NICE 2020 guidance recommends the following AEDs for each type of seizure:

#### *Newly Diagnosed Focal Seizures*

- Offer carbamazepine or lamotrigine as first-line treatment to children, young people, and adults with newly diagnosed focal seizures.<sup>10</sup>
- If carbamazepine or lamotrigine are unsuitable or not tolerated for newly diagnosed focal seizures: offer levetiracetam or oxcarbazepine to women and girls of childbearing potential.<sup>10</sup> Offer levetiracetam, oxcarbazepine or sodium valproate to boys, men and women who are not of childbearing potential.<sup>10</sup> If the first AED tried is ineffective, offer an alternative from these AEDs.<sup>10</sup>
- If first-line treatments for children, young people and adults with focal seizures are ineffective or not tolerated: offer carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine or topiramate as adjunctive treatment to women and girls of childbearing potential.<sup>10</sup> Offer carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate or topiramate as adjunctive treatment to boys, men and women who are not of childbearing potential.<sup>10</sup>

### *Newly Diagnosed Generalized Motor Seizures*

- First-line pharmacologic treatment of newly diagnosed generalized motor seizures (GTC) is sodium valproate for boys, men and women who are not of childbearing potential.<sup>10</sup> Offer lamotrigine if sodium valproate is unsuitable.<sup>10</sup> If the person has myoclonic seizures or is suspected of having juvenile myoclonic epilepsy (JME), be aware that lamotrigine may exacerbate myoclonic seizures.<sup>10</sup> Consider carbamazepine and oxcarbazepine but be aware of the risk of exacerbating myoclonic or absence seizures.<sup>10</sup>
- If first-line treatments for children, young people and adults with GTC seizures are ineffective or not tolerated: offer clobazam, lamotrigine, levetiracetam or topiramate as adjunctive treatment to women and girls of childbearing potential.<sup>10</sup> Offer clobazam, lamotrigine, levetiracetam, sodium valproate or topiramate as adjunctive treatment to boys, men and women who are not of childbearing potential.<sup>10</sup>

### *Newly Diagnosed Absence Seizures*

- For first-line treatment of absence seizures offer ethosuximide to women and girls of childbearing potential.<sup>10</sup>
- Offer ethosuximide or sodium valproate to boys, men and women who are not of childbearing potential. If there is a high risk of GTC seizures, offer sodium valproate first, unless it is unsuitable.<sup>10</sup>
- Offer lamotrigine if ethosuximide and sodium valproate are unsuitable, ineffective or not tolerated.<sup>10</sup>
- Do not offer sodium valproate to women and girls of childbearing potential unless the other options are ineffective or not tolerated and the pregnancy prevention program is in place.<sup>10</sup>

### *Cannabidiol with Clobazam for Treating Seizures Associated with Dravet Syndrome*

Evidence-based recommendations for treating seizures associated with Dravet Syndrome with cannabidiol and clobazam were published by NICE December 2019.<sup>11</sup> Cannabidiol with clobazam is recommended as an option for treating seizures associated with Dravet syndrome in people aged 2 years and older, though, only if the frequency of convulsive seizures is checked every 6 months, and cannabidiol is stopped if the frequency has not fallen by at least 30% compared with the 6 months before starting treatment.<sup>11</sup>

### *Cannabidiol with Clobazam for Treating Seizures Associated with Lennox-Gastaut Syndrome*

Cannabidiol with clobazam for treating seizures associated with LGS was published by NICE December 2019. Cannabidiol with clobazam is recommended as an option for treating seizures associated with LGS in people aged 2 years and older, only if the frequency of drop seizures is checked every 6 months, and cannabidiol is stopped if the frequency has not fallen by at least 30% compared with the 6 months before starting treatment.<sup>12</sup>

### AMERICAN ACADEMY OF NEUROLOGY AND THE AMERICAN EPILEPSY SOCIETY

In 2004, the AAN and AES published guidance on use of 7 second-generation AEDs: gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, and zonisamide. Since the 2004 guideline publication, new studies emerged in the second-generation and more recently approved third-generation AEDs (eslicarbazepine, ezogabine, lacosamide, perampamil, pregabalin, and rufinamide). The FDA has since approved 2 older AEDs (clobazam and vigabatrin) for treating certain types of epileptic disorders in the United States. In 2018, The AAN and AES published guideline updates focused on the efficacy and tolerability of the more recently approved AEDs. Part 1 evaluates evidence for treatment of new-onset epilepsy with newer AEDs.<sup>13</sup> Part 2 evaluates evidence for treatment-resistant epilepsy with newer AEDs.<sup>14</sup>

For the 2018 update, the AAN and AES convened an expert panel which included adult and pediatric epileptologists, methodologic experts, pharmacists, and general neurologists. The 2004 AAN criteria<sup>52</sup> were used to systematically review literature through November 2015, classify pertinent studies according to the therapeutic rating scheme, and link recommendations to evidence strength.<sup>13</sup> The practice guidelines were developed with financial support from the AAN. Significant efforts were made to minimize the potential for conflicts of interest to influence the recommendations of these guidelines.<sup>13</sup> The AAN and AES separated individuals who have a financial stake in the success or failure of the products appraised in the guideline and the developers of the guidelines.<sup>13</sup>

Level A recommendations are considered compelling and accepted by 100% of the author panel.<sup>52</sup> Level B recommendations are considered convincing and accepted by more than 80% of the author panel.<sup>52</sup> Level C recommendations are considered plausible and accepted by more than 50% but less 80% of the author panel.<sup>52</sup>

*Part I: Recommendations for The Use of New AEDs In New-Onset Epilepsy Include:*

- Lamotrigine should (Level B) and levetiracetam and zonisamide may (Level C) be considered in decreasing seizure frequency in adults with new-onset focal epilepsy.<sup>13</sup>
- Lamotrigine should (Level B) and gabapentin may (Level C) be considered in decreasing seizure frequency in patients  $\geq 60$  years of age with new-onset focal epilepsy.<sup>13</sup>
- Unless there are compelling adverse effect–related concerns, ethosuximide or valproic acid should be considered before lamotrigine to decrease seizure frequency in treating absence seizures in childhood absence epilepsy (level B).<sup>13</sup>
- No high-quality studies suggest clobazam, eslicarbazepine, ezogabine, felbamate, gabapentin, lacosamide, levetiracetam, lamotrigine, oxcarbazepine, perampanel, pregabalin, rufinamide, tiagabine, topiramate, vigabatrin, or zonisamide are effective in treating new-onset epilepsy because no high-quality studies exist in adults.<sup>13</sup>

*Part II: Recommendations for The Use of New AEDs In Treatment-Resistant Epilepsy Include:*

- The following are established as effective to reduce seizure frequency (Level A): immediate-release pregabalin and perampanel for treatment-resistant adult focal epilepsy ; vigabatrin for treatment-resistant adult focal epilepsy (not first-line treatment due to side effects); rufinamide for LGS as add-on therapy.<sup>14</sup>
- The following should be considered to decrease seizure frequency (Level B): lacosamide, eslicarbazepine, and extended-release topiramate for treatment-resistant adult focal epilepsy; immediate- and extended-release lamotrigine for generalized epilepsy with treatment-resistant generalized motor seizures in adults; levetiracetam (add-on therapy) for treatment-resistant childhood focal epilepsy (1 month–16 years), treatment-resistant generalized tonic-clonic seizures, and treatment-resistant juvenile myoclonic epilepsy; clobazam for LGS (add-on therapy); zonisamide for treatment-resistant childhood focal epilepsy (6–17 years); oxcarbazepine for treatment-resistant childhood focal epilepsy (1 month–4 years).<sup>14</sup>
- AED selection depends on seizure/syndrome type, patient age, concomitant medications, and tolerability, safety, and efficacy of AED. <sup>14</sup>

**New Formulations or Indications:**

*NEW FORMULATIONS*

- An oral soluble film formulation of clobazam (Sympazan™) received FDA approval in November 2018. Clobazam is indicated for adjunctive treatment of seizures associated with LGS in patients aged 2 years and older.

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- Levetiracetam extended-release tablets (Elevsia XR™) received FDA approval in December 2018. Levetiracetam extended-release tablets are indicated for adjunctive therapy for the treatment of partial onset seizures in patients 12 years of age and older.

#### *NEW FDA-APPROVED INDICATIONS*

- Levetiracetam oral tablets (Keppra®) and levetiracetam extended-release oral tablets (Keppra XR®) received an expanded indication in October 2019 for the treatment of partial-onset seizures in patients 1 month of age and older. Levetiracetam was previously approved as adjunctive therapy for treatment of partial seizures in patients 1 month of age and older.
- Oxcarbazepine extended-release tablets (Oxtellar XR®) received an expanded indication as monotherapy to treat partial-onset seizures in patients 6 years and older in December 2018. Previously, oxcarbazepine was approved as adjunctive treatment for partial-onset seizures in patients 6 years and older.
- Perampanel tablets and oral suspension (Fycompa®) received expanded FDA approval in September 2018 for the treatment of partial-onset seizures with or without secondary generalized seizures in patients 4 years of age and older. Previously, perampanel was FDA-approved for use in patients 12 years of age and older.
- Brivaracetam tablets, oral solution, and intravenous injection (Briviact®) received expanded FDA approval in May 2018 for treatment of partial-onset seizures in patients 4 years of age and older. Previously, brivaracetam was approved for use in patients 16 years of age and older.
- Pregabalin capsules and oral solution (Lyrica®) received expanded FDA approval in May 2019 for adjunctive therapy in the treatment of partial-onset seizures in patients 1 month of age and older. Previously, pregabalin was approved for use in patients 4 years of age and older.
- Vigabatrin (Sabril®) received an expanded indication in January 2020 to include children 2 years of age and older with refractory complex partial seizures. Previously, vigabatrin was approved for patients 10 years age and older.

**New FDA Safety Alerts:**

**Table 1. Description of New FDA Safety Alerts<sup>53</sup>**

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Fosphenytoin Phenytoin	Cerebryx Dilantin	7/2019	Warnings and Precautions	Fosphenytoin and phenytoin can cause severe cutaneous adverse reactions (SCARs), which may be fatal. Reported reactions in phenytoin (the active metabolite of Cerebryx)-treated patients have included toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), acute generalized exanthematous pustulosis (AGEP), and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). The onset of symptoms is usually within 28 days but can occur later. Fosphenytoin or phenytoin should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest a severe cutaneous adverse reaction, use of this drug should not be resumed and alternative therapy should be considered. If a rash occurs, the patient should be evaluated for signs and symptoms of SCARs.
Valproate Sodium, Valproic Acid, Divalproex Sodium	Depacon, Depakene, Depakote	2/2019	Boxed Warning	<p><b>Fetal Risk</b></p> <p>Valproate can cause major congenital malformations, particularly neural tube defects (e.g., spina bifida). In addition, valproate can cause decreased IQ scores and neurodevelopmental disorders following <i>in utero</i> exposure.</p> <p>Valproate is therefore contraindicated for prophylaxis of migraine headaches in pregnant women and in women of childbearing potential who are not using effective contraception. Valproate should not be used to treat women with epilepsy or bipolar disorder who are pregnant or who plan to become pregnant unless other medications have failed to provide adequate symptom control or are otherwise unacceptable.</p>
Perampanel	Fycompa	5/2019	Warnings and Precautions	<p><b>Neurologic Effects</b></p> <p>Prescribers should advise patients against engaging in hazardous activities requiring mental alertness, such as operating motor vehicles or dangerous machinery, until the effect of perampanel is known. Patients should be carefully observed for signs of central nervous system (CNS) depression, such as somnolence and sedation, when perampanel is used with other drugs with sedative properties because of potential additive effects.</p>

Lamotrigine	Lamictal	9/2019	Warnings and Precautions	Hemophagocytic Lymphohistiocytosis Hemophagocytic lymphohistiocytosis (HLH) has occurred in pediatric and adult patients taking lamotrigine for various indications. HLH is a life-threatening syndrome of pathologic immune activation characterized by clinical signs and symptoms of extreme systemic inflammation. It is associated with high mortality rates if not recognized early and treated. Common findings include fever, hepatosplenomegaly, rash, lymphadenopathy, neurologic symptoms, cytopenias, high serum ferritin, hypertriglyceridemia, and liver function and coagulation abnormalities. In cases of HLH reported with lamotrigine, patients have presented with signs of systemic inflammation (fever, rash, hepatosplenomegaly, and organ system dysfunction) and blood dyscrasias. Symptoms have been reported to occur within 8 to 24 days following the initiation of treatment
Gabapentin  Pregabalin	Neurontin, Gralise, Horizant Lyrica Lyrica CR	12/2019	FDA Drug Safety Communication	FDA is warning that serious, life-threatening, and fatal respiratory depression has been reported with the gabapentinoids, gabapentin and pregabalin. Most cases occurred in association with co-administered central nervous system (CNS) depressants, especially opioids, in the setting of underlying respiratory impairment, or in the elderly.
Vigabatrin	Sabril	1/2020	Warnings and Precautions	Intramyelinic edema (IME) has been reported in postmortem examination of infants being treated for infantile spasms (IS) with vigabatrin.

**Randomized Controlled Trials:**

A total of 50 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

**NEW DRUG EVALUATION: Cenobamate (Xcopri™)**

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

**Clinical Efficacy:**

Cenobamate (Xcopri™) tablets are FDA-approved for treatment of partial-onset (focal) seizures in adults.<sup>16</sup> The recommended initial dose of oral cenobamate is 12.5 mg once daily for the first 2 weeks, followed by a slow upward titration: 25 mg once daily for weeks 3 and 4; 50 mg once daily for weeks 5 and 6; 100 mg once daily for weeks 7 and 8; 150 mg once daily for weeks 9 and 10; and 200 mg once daily (the recommended maintenance dose) for week 11 and thereafter.<sup>16</sup> The dose may be further increased by 50 mg once daily every two weeks if necessary based upon response and tolerability, to a maximum dose of 400 mg once daily.<sup>16</sup> The recommended dosage and titration schedule should not be exceeded because of the potential for serious adverse effects including drug reaction with eosinophilia and systemic symptoms (DRESS). When cenobamate is discontinued, the dose should be titrated down gradually over at least two weeks.<sup>16</sup>

Cenobamate is not recommended for patients with severe hepatic impairment or end-stage renal disease undergoing dialysis.<sup>16</sup> The maximum dose should not exceed 200 mg once daily for patients with mild to moderate hepatic impairment.<sup>16</sup> Lower cenobamate doses may be needed for patients with mild to moderate renal disease.<sup>16</sup> The drug is expected to be available in the United States in the second quarter of 2020 following scheduling review by the US Drug Enforcement Administration. Data from an unpublished phase 2 trial involving 222 patients (NCT01397968) and a published phase 2 trial in 437 patients supported the FDA approval of cenobamate.<sup>54</sup>

The published phase 2 study was a multicenter, double-blind, randomized, placebo-controlled, dose-response trial conducted at 107 epilepsy and neurology centers in 16 countries.<sup>15</sup> Adult patients with treatment-resistant focal seizures maintained on 1 to 3 AEDs were randomly assigned (1:1:1:1) to adjuvant once daily oral cenobamate 100 mg, 200 mg, 400 mg, or placebo.<sup>15</sup> Subjects completed an 8-week baseline assessment before starting their assigned therapy. The trial included a 6-week titration phase and 12-week maintenance phase. During the titration phase, all patients began an initial starting dose of cenobamate 100 mg per day that was up-titrated to the target dose, or a matching placebo once daily. After a blinded review of the first 9 patients, the protocol was amended to lower the starting dose of cenobamate to 50 mg per day followed by weekly dose increases of 50 mg up to the target dose. During the 6-week titration phase, if a patient did not tolerate the next higher dose, the dose could be reduced to the previous dose.<sup>15</sup> For the 12-week maintenance phase of the trial, cenobamate dosing was not modified. The dosing regimen used in this trial titrated cenobamate at higher and more rapid doses than the subsequent dosing recommended by the FDA. Patients continued taking their concomitant AED therapy at stabilized doses during the 18-week double blind period. The co-primary efficacy outcomes were percentage change in 28-day focal seizure frequency from baseline and responder rates (percentage of patients achieving  $\geq 50\%$  reduction from baseline in focal seizure frequency) over the 12-week treatment period.<sup>15</sup> Due to different regulatory requirements, the percentage change in focal seizure frequency was considered the primary efficacy outcome for the FDA, and the responder rate was considered the primary efficacy outcome for the European Medicines Agency (EMA).<sup>15</sup> The intention-to-treat (ITT) population included all randomized patients who had taken at least 1 dose of study drug and had any post-baseline seizure data.

Over 12 weeks, significant reductions in seizure frequency were observed with cenobamate compared to placebo in the ITT population. Median seizure frequency reduction from baseline was 24.0% (IQR 45.0 to 7.0%) for the placebo group compared with 35.5% (IQR 62.5 to 5.0%;  $p=0.0071$  vs. placebo) for the 100 mg dose group, and 55.0% for the 200 mg and the 400 mg dose groups (IQR 73.0 to 23.0% and 85.0 to 28.0%, respectively,  $P<0.0001$  vs. placebo for both doses).<sup>15</sup> Significantly more patients had 50% or greater reduction in seizure frequency with cenobamate versus placebo. Responder rates during the 12-week maintenance phase were 25% for the placebo group compared with 40% (OR 1.97, 95% CI 1.08 to 3.56;  $p=0.0365$  vs. placebo) for the 100 mg dose group, 56% (OR 3.74, 95% CI 2.06 to 6.80;  $p<0.0001$  vs. placebo) for the 200 mg dose group, and 64% (OR 5.24, 2.84 to 9.67;  $p<0.0001$  vs. placebo) for the 400 mg dose group.<sup>15</sup> Moderate-quality data from this trial demonstrates adjunctive cenobamate reduced focal seizure frequency, in a dose-related fashion.<sup>15</sup> Adjunctive cenobamate appears to be an effective treatment option in adults with uncontrolled focal seizures when administered for 3 months at a stable maintenance dose.<sup>15</sup> Additional trial information is described and evaluated below in the comparative evidence summary presented in **Table 5**.

Limitations of this study include the short study duration and the potential drug interaction impact of concomitant AEDs. In addition, type of seizure and seizure frequency were self-recorded by the subjects, which could contribute to detection bias.<sup>15</sup> It is not clear if cenobamate is safe and effective in pediatric patients or patients with generalized seizure disorder, as these people were excluded from the phase 2 trial. Two phase 3 trials evaluating the safety and efficacy of cenobamate in patients with generalized motor seizures are currently ongoing.

**Clinical Safety:**

The most common AEs reported in the cenobamate trials which occurred in greater than 10% of patients were dose-dependent somnolence, dizziness, fatigue, and diplopia.<sup>16</sup> Discontinuation rates due to adverse effects were 11%, 9%, and 21% for patients randomized to cenobamate 100 mg, 200 mg and 400 mg once daily compared to 4% of subjects who received placebo.<sup>16</sup> The adverse effects that led to drug discontinuation were ataxia, dizziness, somnolence, diplopia, nystagmus, and vertigo.<sup>16</sup> Specific adverse effect rates in the cenobamate study populations compared to placebo are presented in **Table 4**. One serious case of DRESS occurred in the 200 mg cenobamate group when cenobamate was rapidly titrated.<sup>16</sup> No cases of DRESS were reported when cenobamate was slowly initiated at 12.5 mg once daily and titrated up every 2 weeks to 200 mg once daily.<sup>16</sup> A higher percentage of subjects (31% at 200 mg) had a QT shortening of 20 msec compared to placebo (6 to 17%).<sup>16</sup> Familial short QT syndrome is associated with an increased risk of sudden death and ventricular arrhythmias.<sup>16</sup> No deaths were reported during clinical trials with cenobamate. The FDA also notes that any patient taking an AED should be monitored for the emergence or worsening of depressive symptoms, suicidal thoughts or behaviors, or any other changes in mood.<sup>16</sup> There are limited data regarding the risk of cenobamate use in pregnancy or lactation, but animal data suggests possibility of fetal harm.<sup>16</sup> Currently, an ongoing multicenter, open-label study is being conducted to assess the safety and pharmacokinetics of cenobamate as adjunctive therapy in over 1300 subjects with partial onset seizures (NCT02535091). The cenobamate titration rate is much lower in this trial, with a starting dose of 12.5 mg and dose increases every 2 weeks.

**Table 3. Adverse Reactions Associated with Cenobamate with > 5% Incidence Compared to Placebo<sup>16</sup>**

Adverse Reaction	Cenobamate			Placebo
	100 mg (n=108) %	200 mg (n=223) %	400 mg (n=111) %	n=216 %
Vertigo	1	1	6	1
Diplopia	6	7	15	2
Nausea	6	6	9	3
Constipation	2	4	8	0
Somnolence	19	22	37	11
Dizziness	18	22	33	15
Fatigue	12	14	24	7
Headache	10	12	10	9
Balance Disorder	3	5	9	1
Gait Disturbance	1	3	8	1
Nystagmus	3	7	6	0
Ataxia	2	3	6	2

Cenobamate is extensively metabolized by hepatic enzymes. Consequently, administration of cenobamate can impact the plasma concentrations of other AEDs including lamotrigine, carbamazepine, phenytoin, phenobarbital, and clobazam. In addition, substrates of CYP2C19, CYP3A, and CYP2B6 may interact with cenobamate.

Look-alike / Sound-alike Error Risk Potential: No other medications have been identified

**Comparative Endpoints:**

Clinically Meaningful Endpoints:

- 1) Reduction in seizure frequency
- 2) Increased time of seizure freedom
- 3) Serious adverse events
- 4) Study withdrawal due to an adverse event

Primary Study Endpoint:

- 1) Percentage change in seizure frequency from baseline over 3 months

**Table 4. Pharmacology and Pharmacokinetic Properties.<sup>16</sup>**

Parameter	
Mechanism of Action	Exact mechanism of action unknown: postulated that cenobamate reduces repetitive neuronal firing by inhibiting voltage-gated sodium currents; also, a modulator of the GABA receptor
Oral Bioavailability	88%
Distribution and Protein Binding	Protein Binding: 60%, Volume of Distribution: 40-50 L
Elimination	Clearance: 0.45-9.63 L/hr Excretion: Urine 87.8%; Feces 5.2%
Half-Life	50-60 hrs at doses of 100 to 400 mg once daily
Metabolism	Extensively metabolized; primarily by glucuronidation via UGT2B7 and to a lesser extent by UGT2B4, and by oxidation via CYP2E1, CYP2A6, CYP2B6, and to a lesser extent by CYP2C19 and CYP3A4/5

Abbreviations: GABA= gamma-aminobutyric acid; hrs=hours; L=liter

**Table 5. Comparative Evidence Table.**

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/N NT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Krauss GL, et al. <sup>15</sup>  MC, DB, PC, RCT, Phase 2 trial  N=437	1. Cenobamate 100 mg orally once daily  2. Cenobamate 200 mg orally once daily  3. Cenobamate 400 mg orally once daily  4. Placebo orally once daily  All patients continued concomitant AED regimen during the trial	<u>Demographics:</u> 1. Mean Age: 39 yrs 2. Male: 49% 3. Ethnicity, White: 84% 4. Taking 2-3 AEDs: 74% 5. Most frequently used concomitant AEDs: -levetiracetam: 43% -lamotrigine: 32% -carbamazepine: 30%  <u>Key Inclusion Criteria:</u> 1. Patients aged 18 to 70 years with an ILAE diagnosis of uncontrolled focal epilepsy despite treatment with at least 1 AED within previous 2 years 2. Taking 1-3 AEDs at stable doses at least 4 weeks before screening 3. EEG reading consistent with diagnosis of focal epilepsy 4. Have at least 8 partial seizures during the 8-week baseline period  <u>Key Exclusion Criteria:</u> 1. Patients taking diazepam, phenytoin, or phenobarbital within 1 mo of screening 2. Patients taking vigabatrin within the past 12 months, felbamate for < 18 consecutive mos, or intermittent rescue	<u>ITT:</u> 1. 108 2. 110 3. 111 4. 108  <u>PP:</u> 1. 95 2. 90 3. 81 4. 94  <u>Attrition:</u> 1. 13 (12%) 2. 20 (18%) 3. 30 (27%) 4. 14 (13%)	<u>Co-Primary Endpoints:</u> 1. Median percentage reduction from baseline in focal seizure frequency per 28 days over 12 weeks  1. 35.5% (IQR 62.5 to 15) 2. 55% (IQR 73 to 23) 3. 55% (IQR 85 to 28) 4. 24% (IQR 45 to 7)  P<0.0071 for 100 mg vs. placebo  p <0.0001 for 200 mg and 400 mg vs. placebo  2. 50% or more reduction in seizure frequency per 28 days over 12 weeks (responder).  1. N=41 (40%) 2. N=55 (56%) 3. N=61 (64%) 4. N=26 (25%)  1 vs. 4 OR 1.97 (95% CI 1.08 to 3.56), p<0.0365  2 vs. 4 OR 3.74 (95% CI 2.06 to 6.80), p<0.0001  3 vs. 4 OR 5.24 (95% CI 2.84 to 9.67) p<0.0001  <u>Secondary Endpoint:</u> 1. 75% or more reduction in seizure frequency per 28 days over 12 weeks  1. 17 (17%)	NA  NA  15%/7  31%/4  39%/3	<u>AEs</u> 1. 70 (65%) 2. 84 (76%) 3. 100 (90%) 4. 76 (70%)  <u>SAEs</u> 1. 10 (9%) 2. 4 (4%) 3. 8 (7%) 4. 6 (6%)  <u>AE leading to withdrawal</u> 1. 11 (10%) 2. 15 (14%) 3. 22 (20%) 4. 5 (5%)  p-values and 95% CI NR	NA for all	<b>Risk of Bias (low/high/unclear):</b> <u>Selection Bias:</u> Low. Randomized 1:1:1:1 via IWRS. Computer-generated block size of 4 within each country ensured equal allocation within each group. Baseline demographics similar between groups. <u>Performance Bias:</u> Low. Patients, investigators, and study personnel masked to treatment assignment. Study medication and packaging were identical in appearance to placebo. Side effects from study drug could lead to unblinding. No documentation of how potential drug-drug interactions could have impacted outcomes (seizure frequency or adverse effects). <u>Detection Bias:</u> Unclear. Not clear how seizure frequencies were documented and how they were assessed as they were self-reported by the subjects. <u>Attrition Bias:</u> High. Attrition rates varied by dose. As cenobamate dose increased, rate of AEs leading to study withdrawal increased. <u>Reporting Bias:</u> Unclear. Protocol not available in supplementary materials. <u>Other Bias:</u> Unclear. Funded by SK Life Science, Inc. Funder was responsible for study design and statistical analysis. An employee of SK Life Science is an author for the published study. The employee had a role in data analysis, data interpretation, and writing of the report.  <b>Applicability:</b> <u>Patient:</u> Adults with focal seizures included in study. Twenty-five percent of patients were from the US. Not clear if cenobamate is safe and effective in pediatric patients or generalized seizure disorder. <u>Intervention:</u> Dose ranging trial, titration protocol adjusted due to patient intolerance to higher dosing.

		benzodiazepines within the past month 3. History of status epilepticus within 3 mos of screening 4. History of psychiatric illness within past 2 yrs 5. History of alcoholism or drug misuse within the past 2 yrs		2. 30 (31%) 3. 44 (46%) 4. 10 (10%)  1 vs. 4 p=0.2146 95% CI NR  2 vs. 4 p=0.0003 95% CI NR  3 vs. 4 p<0.0001 95% CI NR	NS  21%/5  36%/3			<p><u>Comparator:</u> Placebo-controlled, cenobamate used as adjunctive therapy in subjects maintained on 1-3 AEDs. Head to head trial with another AED approved for partial seizures (e.g., eslicarbazepine, perampanel, brivaracetam, lacosamide) would be valuable.</p> <p><u>Outcomes:</u> Seizure frequency reduction and responder rate are required by FDA and EMA respectively for drug approval.</p> <p><u>Setting:</u> 107 epilepsy and neurology centers in 16 countries. Number of patients by country:          Australia = 24 (5.5%)          Bulgaria = 37 (8.5%)          Czech Republic = 24 (5.5%)          France = 4 (&lt;1%)          Germany = 33 (7.5%)          Hungary = 15 (3.4%)          Israel = 12 (2.7%)          Poland = 48 (11%)          Romania = 4 (&lt;1%)          Serbia = 28 (6.4%)          South Korea = 31 (7%)          Spain = 27 (6.2%)          Thailand = 8 (1.8%)          Ukraine = 23 (5.3%)          UK = 8 (1.8%)          USA = 111 (25%)</p>
<p><u>Abbreviations</u> AEDs=anti-epileptic drugs; AE=adverse effects; ARR=absolute risk reduction; CI=confidence interval; EEG=electroencephalogram; EMA=European Medication Agency; FDA=Food and Drug Administration; ILAE=International League Against Epilepsy; IQR=interquartile range; ITT=intention to treat; IWRS=interactive web response system; mos=months; N=number of subjects; NA=not applicable; NR=not reported; NNH=number needed to harm; NNT=number needed to treat; PP=per protocol; SAEs=serious adverse effects; yrs=years</p>								

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**Appendix 1: Current Preferred Drug List**

<b>Generic</b>	<b>Brand</b>	<b>Form</b>	<b>Route</b>	<b>PDL</b>	<b>Carveout</b>
carbamazepine	CARBAMAZEPINE	ORAL SUSP	PO	Y	
carbamazepine	TEGRETOL	ORAL SUSP	PO	Y	
carbamazepine	CARBAMAZEPINE	TAB CHEW	PO	Y	
carbamazepine	CARBAMAZEPINE ER	TAB ER 12H	PO	Y	
carbamazepine	TEGRETOL XR	TAB ER 12H	PO	Y	
carbamazepine	CARBAMAZEPINE	TABLET	PO	Y	
carbamazepine	EPITOL	TABLET	PO	Y	
carbamazepine	TEGRETOL	TABLET	PO	Y	
diazepam	DIASTAT	KIT	RC	Y	
diazepam	DIASTAT ACUDIAL	KIT	RC	Y	
diazepam	DIAZEPAM	KIT	RC	Y	
divalproex sodium	DEPAKOTE SPRINKLE	CAP DR SPR	PO	Y	Y
divalproex sodium	DIVALPROEX SODIUM	CAP DR SPR	PO	Y	Y
divalproex sodium	DEPAKOTE ER	TAB ER 24H	PO	Y	Y
divalproex sodium	DIVALPROEX SODIUM ER	TAB ER 24H	PO	Y	Y
divalproex sodium	DEPAKOTE	TABLET DR	PO	Y	Y
divalproex sodium	DIVALPROEX SODIUM	TABLET DR	PO	Y	Y
ethosuximide	ETHOSUXIMIDE	CAPSULE	PO	Y	
ethosuximide	ZARONTIN	CAPSULE	PO	Y	
ethosuximide	ETHOSUXIMIDE	SOLUTION	PO	Y	
ethosuximide	ZARONTIN	SOLUTION	PO	Y	
ethotoin	PEGANONE	TABLET	PO	Y	
gabapentin	GABAPENTIN	CAPSULE	PO	Y	
gabapentin	NEURONTIN	CAPSULE	PO	Y	
gabapentin	GABAPENTIN	TABLET	PO	Y	
gabapentin	NEURONTIN	TABLET	PO	Y	
lacosamide	VIMPAT	TABLET	PO	Y	
lamotrigine	LAMICTAL	TABLET	PO	Y	Y
lamotrigine	LAMOTRIGINE	TABLET	PO	Y	Y
lamotrigine	SUBVENITE	TABLET	PO	Y	Y
levetiracetam	KEPPRA	SOLUTION	PO	Y	
levetiracetam	LEVETIRACETAM	SOLUTION	PO	Y	
levetiracetam	KEPPRA	TABLET	PO	Y	
levetiracetam	LEVETIRACETAM	TABLET	PO	Y	
levetiracetam	ROWEEPRA	TABLET	PO	Y	
methsuximide	CELONTIN	CAPSULE	PO	Y	
oxcarbazepine	OXCARBAZEPINE	ORAL SUSP	PO	Y	
oxcarbazepine	TRILEPTAL	ORAL SUSP	PO	Y	

oxcarbazepine	OXCARBAZEPINE	TABLET	PO	Y	
oxcarbazepine	TRILEPTAL	TABLET	PO	Y	
phenobarbital	PHENOBARBITAL	ELIXIR	PO	Y	
phenobarbital	PHENOBARBITAL	TABLET	PO	Y	
phenytoin	DILANTIN-125	ORAL SUSP	PO	Y	
phenytoin	PHENYTOIN	ORAL SUSP	PO	Y	
phenytoin	DILANTIN	TAB CHEW	PO	Y	
phenytoin	PHENYTOIN	TAB CHEW	PO	Y	
phenytoin sodium extended	DILANTIN	CAPSULE	PO	Y	
phenytoin sodium extended	PHENYTEK	CAPSULE	PO	Y	
phenytoin sodium extended	PHENYTOIN SODIUM EXTENDED	CAPSULE	PO	Y	
primidone	MYSOLINE	TABLET	PO	Y	
primidone	PRIMIDONE	TABLET	PO	Y	
rufinamide	BANZEL	TABLET	PO	Y	
tiagabine HCl	GABITRIL	TABLET	PO	Y	
tiagabine HCl	TIAGABINE HCL	TABLET	PO	Y	
topiramate	TOPAMAX	TABLET	PO	Y	
topiramate	TOPIRAMATE	TABLET	PO	Y	
valproic acid	VALPROIC ACID	CAPSULE	PO	Y	Y
valproic acid (as sodium salt)	VALPROIC ACID	SOLUTION	PO	Y	Y
zonisamide	ZONISAMIDE	CAPSULE	PO	Y	
lamotrigine	LAMICTAL (BLUE)	TAB DS PK	PO	V	Y
lamotrigine	LAMICTAL (GREEN)	TAB DS PK	PO	V	Y
lamotrigine	LAMICTAL (ORANGE)	TAB DS PK	PO	V	Y
lamotrigine	LAMOTRIGINE (BLUE)	TAB DS PK	PO	V	Y
lamotrigine	LAMOTRIGINE (GREEN)	TAB DS PK	PO	V	Y
lamotrigine	LAMOTRIGINE (ORANGE)	TAB DS PK	PO	V	Y
lamotrigine	SUBVENITE (BLUE)	TAB DS PK	PO	V	Y
lamotrigine	SUBVENITE (GREEN)	TAB DS PK	PO	V	Y
lamotrigine	SUBVENITE (ORANGE)	TAB DS PK	PO	V	Y
lamotrigine	LAMICTAL XR	TAB ER 24	PO	V	Y
lamotrigine	LAMOTRIGINE ER	TAB ER 24	PO	V	Y
lamotrigine	LAMICTAL ODT	TAB RAPDIS	PO	V	Y
lamotrigine	LAMOTRIGINE ODT	TAB RAPDIS	PO	V	Y
lamotrigine	LAMICTAL	TB CHW DSP	PO	V	Y
lamotrigine	LAMOTRIGINE	TB CHW DSP	PO	V	Y
lamotrigine	LAMICTAL XR (BLUE)	TB ER DSPK	PO	V	Y
lamotrigine	LAMICTAL XR (GREEN)	TB ER DSPK	PO	V	Y
lamotrigine	LAMICTAL XR (ORANGE)	TB ER DSPK	PO	V	Y
lamotrigine	LAMICTAL ODT (BLUE)	TB RD DSPK	PO	V	Y

lamotrigine	LAMICTAL ODT (GREEN)	TB RD DSPK	PO	V	Y
lamotrigine	LAMICTAL ODT (ORANGE)	TB RD DSPK	PO	V	Y
lamotrigine	LAMOTRIGINE ODT (BLUE)	TB RD DSPK	PO	V	Y
lamotrigine	LAMOTRIGINE ODT (GREEN)	TB RD DSPK	PO	V	Y
lamotrigine	LAMOTRIGINE ODT (ORANGE)	TB RD DSPK	PO	V	Y
brivaracetam	BRIVIACT	SOLUTION	PO	N	
brivaracetam	BRIVIACT	TABLET	PO	N	
cannabidiol (CBD)	EPIDIOLEX	SOLUTION	PO	N	
carbamazepine	CARBAMAZEPINE ER	CPMP 12HR	PO	N	
carbamazepine	CARBATROL	CPMP 12HR	PO	N	
clobazam	SYMPAZAN	FILM	PO	N	
clobazam	CLOBAZAM	ORAL SUSP	PO	N	
clobazam	ONFI	ORAL SUSP	PO	N	
clobazam	CLOBAZAM	TABLET	PO	N	
clobazam	ONFI	TABLET	PO	N	
eslicarbazepine acetate	APTIOM	TABLET	PO	N	
felbamate	FELBAMATE	ORAL SUSP	PO	N	
felbamate	FELBATOL	ORAL SUSP	PO	N	
felbamate	FELBAMATE	TABLET	PO	N	
felbamate	FELBATOL	TABLET	PO	N	
gabapentin	GABAPENTIN	SOLUTION	PO	N	
gabapentin	NEURONTIN	SOLUTION	PO	N	
gabapentin	GRALISE	TAB ER 24H	PO	N	
gabapentin enacarbil	HORIZANT	TABLET ER	PO	N	
gabapentin/lidocaine	GABACAINE	KIT	MC	N	
lacosamide	VIMPAT	SOLUTION	PO	N	
lacosamide	VIMPAT	TAB DS PK	PO	N	
levetiracetam	KEPPRA XR	TAB ER 24H	PO	N	
levetiracetam	LEVETIRACETAM ER	TAB ER 24H	PO	N	
levetiracetam	ROWEEPRA XR	TAB ER 24H	PO	N	
levetiracetam	SPRITAM	TAB SUSP	PO	N	
midazolam	NAYZILAM	SPRAY	NS	N	
oxcarbazepine	OXTELLAR XR	TAB ER 24H	PO	N	
perampanel	FYCOMPA	ORAL SUSP	PO	N	
perampanel	FYCOMPA	TAB DS PK	PO	N	
perampanel	FYCOMPA	TABLET	PO	N	
pregabalin	LYRICA	CAPSULE	PO	N	
pregabalin	PREGABALIN	CAPSULE	PO	N	
pregabalin	LYRICA	SOLUTION	PO	N	
pregabalin	PREGABALIN	SOLUTION	PO	N	

rufinamide	BANZEL	ORAL SUSP	PO	N	
stiripentol	DIACOMIT	CAPSULE	PO	N	
stiripentol	DIACOMIT	POWD PACK	PO	N	
topiramate	TROKENDI XR	CAP ER 24H	PO	N	
topiramate	QUDEXY XR	CAP SPR 24	PO	N	
topiramate	TOPIRAMATE ER	CAP SPR 24	PO	N	
topiramate	TOPAMAX	CAP SPRINK	PO	N	
topiramate	TOPIRAMATE	CAP SPRINK	PO	N	
vigabatrin	SABRIL	POWD PACK	PO	N	
vigabatrin	VIGABATRIN	POWD PACK	PO	N	
vigabatrin	VIGADRONE	POWD PACK	PO	N	
vigabatrin	SABRIL	TABLET	PO	N	
vigabatrin	VIGABATRIN	TABLET	PO	N	
carbamazepine	EQUETRO	CPMP 12HR	PO		Y
phenobarbital	PHENOBARBITAL	ELIXIR	PO		

## Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to November Week 5 2020, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations February 11, 2020

1	Carbamazepine	4733
2	Diazepam/	3225
3	divalproex.mp. or Valproic Acid/	6988
4	Ethosuximide/	224
5	ethoin.mp.	2
6	lacosamide.mp.	772
7	lamotrigine.mp.	4081
8	levetiracetam.mp.	3355
9	methsuximide.mp.	12
10	oxcarbazepine.mp.	1501
11	Phenobarbital/	2109
12	Phenytoin/	2372
14	Primidone/	106
14	rufinamide.mp.	240
15	tiagabine.mp.	594
16	topiramate.mp.	3849
17	Valproic Acid/	6759
18	zonisamide.mp.	997
19	brivaracetam.mp.	231
20	clobazam.mp.	534
21	eslicarbazepine.mp.	2
22	felbamate.mp.	325
23	perampanel.mp.	434
24	Pregabalin/	1714
25	Vigabatrin/	663
26	Gabapentin	2655
27	midazolam spray.mp	9
28	stiripentol.mp	177
29	Cannabidiol/	1077
30	cenobamate.mp	7
31	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30: 33279	
32	Epilepsy/	33169
33	31 and 32	4602
34	limit 29 to (english language and humans and yr="2018 -Current" and (clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews))	50

## Appendix 3: Prescribing Information Highlights

### HIGHLIGHTS OF PRESCRIBING INFORMATION

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

**XCOPRI® (cenobamate tablets), for oral use, [controlled substance schedule pending]**

**Initial U.S. Approval: XXXX [pending controlled substance scheduling]**

#### INDICATIONS AND USAGE

XCOPRI is indicated for the treatment of partial-onset seizures in adult patients. (1)

#### DOSAGE AND ADMINISTRATION

- Swallow tablets whole. Do not crush or chew. (2.1)
- The recommended initial dosage of XCOPRI is 12.5 mg once daily, titrated to the recommended maintenance dosage of 200 mg once daily. The recommended titration schedule should not be exceeded. The maximum dosage is 400 mg once daily. (2.2)
- Hepatic impairment: For patients with mild or moderate hepatic impairment, the maximum recommended dosage is 200 mg once daily. (2.3, 8.7, 12.3)

#### DOSAGE FORMS AND STRENGTHS

- Tablets: 12.5 mg, 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg. (3)

#### CONTRAINDICATIONS

- Hypersensitivity to cenobamate or any of the inactive ingredients in XCOPRI. (4)
- Familial Short QT syndrome. (4)

#### WARNINGS AND PRECAUTIONS

- *Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/ Multi-Organ Hypersensitivity*: Discontinue if no alternate etiology. (5.1)
- *QT Shortening*: Use caution when administering XCOPRI with other drugs that shorten the QT interval (5.2)
- *Suicidal Behavior and Ideation*: Monitor patients for suicidal behavior and ideation. (5.3)
- *Neurological Adverse Reactions*: Monitor for somnolence and fatigue and advise patients not to drive or operate machinery until they have gained sufficient experience on XCOPRI. Concomitant use with other CNS depressants or alcohol may have additive effects. (5.4)

- *Withdrawal of Antiepileptic Drugs*: XCOPRI should be gradually withdrawn to minimize the potential of increased seizure frequency. (5.5)

#### ADVERSE REACTIONS

The most common adverse reactions in patients receiving XCOPRI (at least 10% for XCOPRI and more frequently than placebo) include somnolence, dizziness, fatigue, diplopia, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact SK Life Science, Inc. at 1-866-657-5574 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

#### DRUG INTERACTIONS

- Phenytoin: Gradually decrease phenytoin dosage by up to 50% (7.1)
- Phenobarbital and Clobazam: Reduce dosage as needed when used concomitantly with XCOPRI. (7.1)
- Lamotrigine, Carbamazepine: Increase dosage as needed when used concomitantly with XCOPRI. (7.1)
- CYP2B6 and CYP3A Substrates: Increase dosage as needed when used concomitantly with XCOPRI. (7.1)
- CYP2C19 Substrates: Reduce dosage as needed when used concomitantly with XCOPRI. (7.1)
- Oral Contraceptives: Effectiveness of hormonal oral contraceptives may be reduced when administered concomitantly with XCOPRI. Women should use additional or alternative non-hormonal birth control. (7.1)

#### USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Renal Impairment: Use with caution and dosage reduction may be considered in patients with mild to moderate (CLcr 30 to < 90 mL/min) and severe (CLcr < 30 mL/min) renal impairment. Use not recommended in end-stage renal disease (CLcr < 15 mL/min) undergoing dialysis. (8.6)
- Hepatic Impairment: Use with caution in patients with mild to moderate hepatic impairment; lower maximum dosage and additional dosage reduction may be considered. Use of XCOPRI in patients with severe hepatic impairment is not recommended. (2.3, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2019

Appendix 4: Prior Authorization Criteria

## Cannabidiol

**Goal(s):**

- To ensure appropriate drug use and restrict to indications supported by medical literature.

**Length of Authorization:**

- Up to 12 months

**Requires PA:**

- Cannabidiol

**Covered Alternatives:**

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for renewal of therapy previously approved by the FFS system?	<b>Yes:</b> Go to <b>Renewal Criteria</b>	<b>No:</b> Go to #3
3. Is this an FDA approved indication? (Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older).	<b>Yes:</b> Go to #4	<b>No:</b> Pass to RPh. Deny; medical appropriateness

<b>Approval Criteria</b>		
<p>4. Is the patient uncontrolled on current baseline therapy with at least one other antiepileptic medication? AND Is cannabidiol intended to be prescribed as adjuvant antiepileptic therapy?</p>	<p><b>Yes:</b> Go to #5</p>	<p><b>No:</b> Pass to RPh. Deny; medical appropriateness</p>
<p>5. Is the prescribed dose greater than 20mg/kg/day?</p>	<p><b>Yes:</b> Pass to RPh. Deny; medical appropriateness</p>	<p><b>No:</b> Go to # 6</p>
<p>6. Are baseline liver function tests (LFTs) on file (serum transaminases and total bilirubin levels)?</p> <p>AND</p> <p>If LFTs are not within normal limits has the cannabidiol dose been adjusted per guidance for moderate to severe hepatic impairment in Table 1?</p> <p>LFTs should be obtained at 1 month, 3 months, and 6 months after starting treatment with cannabidiol and periodically thereafter as clinically indicated, after cannabidiol dose changes, or addition of other medications that are known to impact the liver.</p>	<p><b>Yes:</b> Approve for 12 months</p> <p>Document results here:  Date of lab work _____  AST _____  ALT _____  Total Bilirubin _____</p>	<p><b>No:</b> Pass to RPh. Deny; medical appropriateness</p>

## Renewal Criteria

<p>1. Are recent LFT's documented in patient records?</p> <p>AND</p> <p>If LFTs are not within normal limits has the cannabidiol dose been adjusted per guidance for moderate to severe hepatic impairment in Table 1?</p>	<p><b>Yes:</b> Go to # 2</p> <p>Document results here:</p> <p>Date of lab work_____</p> <p>AST_____</p> <p>ALT_____</p> <p>Total Bilirubin_____</p>	<p><b>No:</b> Pass to RPh. Deny; medical appropriateness</p>
<p>2. Has seizure frequency decreased since beginning therapy?</p>	<p><b>Yes:</b> Go to #3</p>	<p><b>No:</b> Pass to RPh. Deny for lack of treatment response.</p>
<p>3. Is the prescribed dose greater than 20mg/kg/day?</p>	<p><b>Yes:</b> Pass to RPh. Deny; medical appropriateness</p>	<p><b>No:</b> Go to # 4</p>
<p>4. Is cannabidiol intended to be prescribed as adjuvant antiepileptic therapy?</p>	<p><b>Yes:</b> Approve for 12 months</p>	<p><b>No:</b> Pass to RPh. Deny; medical appropriateness</p>

**Table 1: Dose Adjustments of Cannabidiol in Patients with Hepatic Impairment<sup>1</sup>**

Hepatic Impairment	Starting Dosage	Maintenance Dosage	Maximum Recommended Dosage
<b>Mild</b>	2.5 mg/kg twice daily (5 mg/kg/day)	5 mg/kg twice daily (10 mg/kg/day)	10 mg/kg twice daily (20 mg/kg/day)
<b>Moderate</b>	1.25 mg/kg twice daily (2.5 mg/kg/day)	2.5 mg/kg twice daily (5 mg/kg/day)	5 mg/kg twice daily (10 mg/kg/day)
<b>Severe</b>	0.5 mg/kg twice daily (1 mg/kg/day)	1 mg/kg twice daily (2 mg/kg/day)	2 mg/kg twice daily (4 mg/kg/day)

1. Epidolex (cannabidiol) Oral Solution Prescribing Information. Carlsbad, CA; Greenwich Biosciences, Inc. June 2018.

P&T/DUR Review: [6/2020 \(DM\)](#); 3/19; 1/19 (DM)

Implementation: 5/1/19; 3/1/19

## Clobazam

**Goal(s):** To ensure appropriate drug use and restrict to indications supported by medical literature and funded by Oregon Health Plan.

**Length of Authorization:**

- 12 months

**Requires PA:**

Clobazam

**Covered Alternatives:**

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

### Approval Criteria

1. What diagnosis is being treated?	Record ICD10 code
-------------------------------------	-------------------

Approval Criteria		
2. Is the request for renewal of therapy previously approved by the FFS system?	<b>Yes:</b> Go to <b>Renewal Criteria</b>	<b>No:</b> Go to #3
3. Does the patient have a diagnosis of Lennox-Gastaut syndrome and is the patient 2 years of age or older?	<b>Yes:</b> Go to #3	<b>No:</b> Go to # 5
4. Is the patient uncontrolled on current baseline therapy with at least one other antiepileptic medication?	<b>Yes:</b> Approve for 12 months	<b>No:</b> Pass to RPh. Deny; medical appropriateness
5. Does the patient have a diagnosis of Dravet Syndrome and is the patient 2 years of age or older?	<b>Yes:</b> Approve for 12 months	<b>No:</b> Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Has seizure frequency decreased since beginning therapy?	<b>Yes:</b> Approve for 12 months	<b>No:</b> Pass to RPh. Deny for lack of treatment response.

*Limitations of Use:*

- Clobazam is not FDA-approved for epilepsy syndromes other than Lennox-Gastaut.
- National Institute for Health and Care Excellence (NICE) guidance recommends clobazam as a second line agent for management of Dravet Syndrome.<sup>1</sup>

1.National Institute for Health and Care Excellence (NICE). Epilepsies: diagnosis and management. nice.org.uk/guidance/cg137. Accessed July 30, 2018

P&T Review: 6/2020 (DM); 1/19 (DM); 3/18; 7/16; 3/15; 5/12  
 Implementation: 3/1/19; 8/16, 8/12

## Pregabalin

**Goal(s):**

- Provide coverage only for funded Oregon Health Plan diagnoses that are supported by the medical literature.

**Length of Authorization:**

- 90 days to lifetime (criteria-specific)

**Requires PA:**

- Pregabalin and pregabalin extended release

**Covered Alternatives**

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the request for pregabalin immediate release?	<b>Yes:</b> Go to # 3	<b>No:</b> Go to #4
3. Does the patient have a diagnosis of epilepsy?	<b>Yes:</b> Approve for lifetime	<b>No:</b> Go to # 4
4. Is the diagnosis an OHP-funded diagnosis with evidence supporting its use in that condition (see Table 1 below for examples)?	<b>Yes:</b> Approve for 90 days, with subsequent approvals dependent on documented positive response for lifetime approval.	<b>No:</b> Pass to RPh. Deny; not funded by the OHP.

**Table 1. OHP Funded Diagnosis and Evidence Supports Drug Use in Specific Indication**

Condition	Pregabalin	Pregabalin Extended-Release
Funded		
Diabetic Neuropathy	X	X
Postherpetic Neuropathy	X	X
Painful Polyneuropathy	X	
Spinal Cord Injury Pain	X	
Chemotherapy Induced Neuropathy	X	
Non-funded		
Fibromyalgia	X	

P&T Review: [6/2020 \(DM\)](#); 1/19 (DM); 7/18; 3/17; 3/15; 5/09; 9/07; 11/07  
 Implementation: 10/18, 4/18/15; 1/11; 1/10

## Stiripentol

**Goal(s):**

- To ensure appropriate drug use and restrict to indications supported by medical literature and funded by Oregon Health Plan.

**Length of Authorization:**

- Up to 12 months

**Requires PA:**

- Stiripentol capsules and powder for oral suspension

**Covered Alternatives:**

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

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

Approval Criteria		
2. Is the request for renewal of therapy previously approved by the FFS system?	<b>Yes:</b> Go to <b>Renewal Criteria</b>	<b>No:</b> Go to #3
3. Is the request for the FDA approved indication of Dravet syndrome in patients 2 years of age and older taking clobazam?	<b>Yes:</b> Go to #3	<b>No:</b> Pass to RPh. Deny; medical appropriateness
4. Are baseline white blood cell (WBC) and platelet counts on file within the past 3 months?  <u>Note:</u> Labs should be assessed every six months while receiving stiripentol therapy.	<b>Yes:</b> Approve for 12 months  Document results here: Date of lab work _____ WBC _____ Platelets _____	<b>No:</b> Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Are recent WBC and platelet counts documented in patient records?  <u>Note:</u> Labs should be assessed every six months while receiving stiripentol therapy.	<b>Yes:</b> Go to # 2  Document results here: Date of lab work _____ WBC _____ Platelets _____	<b>No:</b> Pass to RPh. Deny; medical appropriateness
2. Has seizure frequency decreased since beginning therapy?	<b>Yes:</b> Approve for 12 months	<b>No:</b> Pass to RPh. Deny for lack of treatment response.

P&T/DUR Review: 6/2020 (DM); 1/19 (DM)  
Implementation: 3/1/2019

## Topiramate

**Goal(s):**

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

**Length of Authorization:**

- 90 days to lifetime

**Requires PA:**

Non-preferred topiramate products

**Covered Alternatives:**

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

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

Approval Criteria		
<p>5. Has the patient tried or are they contraindicated to at least two of the following drugs?</p> <ul style="list-style-type: none"> <li>• Lithium</li> <li>• Valproate and derivatives</li> <li>• Lamotrigine</li> <li>• Carbamazepine</li> <li>• Atypical antipsychotic</li> </ul> <p>Document drugs tried or contraindications.</p>	<p><b>Yes:</b> Approve for 90 days with subsequent approvals dependent on documented positive response for lifetime approval.</p>	<p><b>No:</b> Pass to RPh; Deny; medical appropriateness. Recommend trial of 2 covered alternatives.</p>
<p>6. Is the patient using the medication for weight loss? (Obesity ICD10 E669; E6601)?</p>	<p><b>Yes:</b> Pass to RPh. Deny; not funded by the OHP</p>	<p><b>No:</b> Pass to RPh. Go to #7</p>
<p>7. All other indications need to be evaluated for appropriateness:</p> <ul style="list-style-type: none"> <li>• Neuropathic pain</li> <li>• Post-Traumatic Stress Disorder (PTSD)</li> <li>• Substance abuse</li> </ul>	<p>Use is off-label: Deny; medical appropriateness. Other treatments should be tried as appropriate.            Use is unfunded: Deny; not funded by the OHP.            If clinically warranted: Deny; medical appropriateness. Use clinical judgment to approve for 1 month to allow time for appeal.  <b>MESSAGE:</b> "Although the request has been denied for long-term use because it is considered medically inappropriate, it has also been APPROVED for one month to allow time for appeal."</p>	

P&T Review: 6/2020 (DM); 5/19 (KS); 1/19 (DM); 7/18; 3/18; 3/17; 7/16; 3/15; 2/12; 9/07; 11/07  
 Implementation: 4/18/15; 5/12, 1/12

## Drug Use Evaluation: Fluoroquinolone Safety

**Date of Review:** June 2020

### Research Questions:

1. What are the common indications for fluoroquinolone (FQ) antibiotic claims in the Oregon Health Plan (OHP) Fee-for-Service (FFS) adult and pediatric populations?
2. Are FQ antibiotics associated with increased risk of harm based on medical claims data in the OHP FFS adult and pediatric populations?
3. What proportion of OHP FFS patients have comorbidities which may put them at increased risk of adverse events from a FQ antibiotic?

### Conclusions:

- Published safety data since 2015 have identified serious adverse effects associated with FQ use that may justify policy changes in the OHP FFS program.
- Fluoroquinolone adverse events that resulted in labeling changes and were considered the adverse events of interest were: disabling effects on tendon, muscle joints, nerves, central nervous system, hypoglycemia, mental health concerns (e.g., disorientation, nervousness, restlessness, mild cognitive impairment and delirium), aortic aneurysm and death.
- Patients of any age in the fee-for-service (FFS) Oregon Medicaid population with an oral FQ claim from the preferred drug list (PDL) class from January 1, 2018 to December 31, 2018 were included.
- In 2018, 1,209 patients had a claim for either ciprofloxacin (69.1%) or levofloxacin (30.9%). Thirty two percent of patients with a FQ claim had an adverse event known to be associated with FQ use (e.g., hypoglycemia, mental health concerns, tendonitis, joint pain, or death). However, the number of the identified adverse events was similar 6 months before the first FQ claim and 6 months after the first FQ claim (19.4% vs. 21.3%, respectively).
- 26.5% of patients with a FQ claim had a comorbidity associated with increased risk of a FQ-related adverse reaction. Diabetes (13.2%) and hypertension (20.4%) were the most common comorbidities. Incidence of adverse effects were more common in patients with a comorbidity (50%) compared to patients without a comorbidity (32.4%).
- Antibiotic use 30-days prior to FQ claim was low (15.2%), suggesting the FQ may have been used as a first-line option. Patients with an antibiotic allergy diagnosis accounted for 8.6% of patients, which would not explain the high utilization of FQs as first-line therapy. This is concerning since FQ are recommended as an alternative treatment option in most patients due to risk for serious adverse events.
- This OHP FFS FQ use evaluation does not provide sufficient evidence that FQ use is associated with increased adverse events in this population.

### Recommendations:

- No policy changes are recommended at this time.

**Background:**

The Food and Drug Administration (FDA) issued the first safety warning in 2016 for the FQ class, followed by 3 additional warnings of serious adverse reactions with the use of FQs (Table 1).<sup>1-4</sup> The risk applies to all dosage forms of FQ and appears to be a class effect. It is recommended that FQs only be used when benefit outweighs the risk of treatment.

**Table 1. FDA Warnings for Fluoroquinolone Antibiotics**

Year	Warning	Recommendation
5/2016 <sup>1</sup>	- Disabling and permanent side effects involving tendons, muscles, joints, nerves and central nervous system.	Risk may outweigh benefits; limit use in acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections.
7/2016 <sup>2</sup>	- Same as above	FDA updated prescribing information to include a boxed label
7/2018 <sup>3</sup>	- Significant hypoglycemia and certain mental health adverse reactions (e.g., disorientation, nervousness, mild cognitive impairment, delirium) - Older individuals and patients with diabetes taking medications to reduce blood sugars are at highest risk	Updated boxed warning in prescribing information
12/2018 <sup>4</sup>	- Increased risk of aortic aneurysm leading to bleeding and possible death - Patients at greatest risk are those with history of certain blockages or aneurysms of the aorta or other blood vessels, high blood pressure, Marfan syndrome, Ehlers-Danlos syndrome and the elderly	Updated boxed warning in prescribing information

Routine use of FQ in the outpatient setting has declined due to multiple adverse reactions. The FDA recommends against the use of FQ therapy first-line for acute sinusitis and acute bronchitis and uncomplicated urinary tract infections (UTI). Fluoroquinolones can be used as alternate treatment for acute sinusitis, adult acute otitis media, and mammalian bites. Ciprofloxacin and levofloxacin are the only available oral antibiotics which can treat susceptible strains of *Pseudomonas aeruginosa*.

Ciprofloxacin and levofloxacin (branded and generic formulations) are the only preferred oral agents in the FQ PDL. There were 215 claims in the third quarter of 2019 for ciprofloxacin and 88 for levofloxacin. There are no clinical PA criteria for this class.

**Methods:**

Patients of any age were included if they had a paid OHP FFS pharmacy claim for an oral FQ from January 1, 2018 to December 31, 2018. Diagnoses for FDA-approved conditions (as defined in Table 2) were identified based on medical claims within 15 days of the first FQ claim (reference claim) in the reporting period. If patients had medical claims with multiple infectious diagnoses in that period, they may be counted more than once. Patients with any FQ claim were included. To ensure complete reporting, patients were only included if they had at least 75% Medicaid eligibility in the 6 months before and after the reference claim. Patients were excluded if they had Medicare Part D.

Baseline demographic information (e.g., patient age, gender, race, etc.) was collected based on the reference claim in the defined reporting period above. Comorbidities identified by the FDA as increasing the risk of a severe adverse reaction (Table 2) were identified in the 6 months before and after the reference claim. Medical claims for adverse reactions, that are commonly associated with FQ use, were recorded if they occurred at any time 6 months prior or 6 months after the reference claim (Table 3). Adverse events were further categorized as occurring 6 months before or 6 months after the first FQ in the reporting period (Table 4). Antibiotic claims within the previous 30 days will be analyzed to determine if the first FQ claim was used for first-line therapy (Table 5). Prescriber specialty was identified based on primary provider taxonomy (Table 6). The number of day's supply of FQ before and after the reference claim is displayed in Table 7.

**Results:**

Most patients with a FQ claim in 2018 were white (37%), adults (90.5%) and female (71.5%). All FQ claims were for ciprofloxacin (69.1%) or levofloxacin (30.9%). Comorbid diabetes and hypertension, which may increase the risk of an FQ-related adverse event, were identified in 13.2% and 20.4% of patients, respectively. All other high-risk comorbidities were uncommon (<1%) (Table 2). In an effort to correlate FQ use with a medical diagnosis, medical claims 15 days before the FQ reference claim were analyzed. About 42.4% of patients were found to have at least one of the 10 identified infections and 62.8% had a different type of infection (Table 2). The predominant identified diagnosis was UTIs (17%), cystitis (9.0%) and pneumonia (7.8%). The high number of claims for UTIs and cystitis is somewhat concerning since the FDA recommends against the use of FQ first line for uncomplicated infections of this type.

**Table 2. Demographics.**

	Number of Patients (n=1,209)	Percent
Age	Avg age: 38 years	
<ul style="list-style-type: none"> <li>• ≤ 18 years</li> <li>• &gt; 18 years</li> </ul>	115 1,094	9.5% 90.5%
Gender		
<ul style="list-style-type: none"> <li>• Female</li> <li>• Male</li> </ul>	865 344	71.5% 28.5%
Race		
<ul style="list-style-type: none"> <li>• White</li> <li>• Black</li> <li>• Unknown</li> <li>• Other</li> </ul>	448 6 290 465	37.1% 0.5% 24.0% 38.5%
Comorbidities 6 months prior to reference claim:		
<ul style="list-style-type: none"> <li>• Diabetes diagnosis (ICD-10: E08x, E10x, E11x, E13x)</li> <li>• Age ≥ 70 years</li> <li>• Aortic aneurysm (ICD-10: I71x)</li> <li>• Aneurysm (ICD-10: I72x)</li> <li>• Hypertension diagnosis (ICD-10: I10, I15x)</li> </ul>	159 4 5 1 247	13.2% 0.3% 0.4% 0.1% 20.4%

<ul style="list-style-type: none"> <li>• Marfan syndrome (ICD-10: Q87.4x, Q87.10))</li> <li>• Ehlers-Danlos syndrome (ICD-10: Q79.6x)</li> </ul>	0 3	0% 0.2%
<b>Fluoroquinolone Claims</b> <ul style="list-style-type: none"> <li>• Ciprofloxacin</li> <li>• Levofloxacin</li> <li>• Moxifloxacin</li> <li>• Other</li> </ul>	836 373 0 0	69.1% 30.9% 0% 0%
<b>Diagnosis 15 days before reference claim:</b> <ul style="list-style-type: none"> <li>• Urinary tract infection (ICD-10: N39.0)</li> <li>• Upper respiratory infection (ICD-10: J06.9)</li> <li>• Pyelonephritis (ICD-10: N10, N11.1)</li> <li>• Otitis media (ICD-10: H66x, H67x)</li> <li>• Mammalian bites (ICD-10: W55x, W540x)</li> <li>• Acute sinusitis (ICD-10: J01x)</li> <li>• Chronic sinusitis (ICD-10: J32x)</li> <li>• Acute bronchitis (ICD-10: J20x)</li> <li>• Chronic bronchitis (ICD-10: J40, J41x, J42)</li> <li>• Pneumonia (J13x-J18x)</li> <li>• None of the above identified</li> </ul> <ul style="list-style-type: none"> <li>• Most common infectious diagnoses, if none of the above were identified, with an occurrence of <math>\geq 1\%</math>: <ul style="list-style-type: none"> <li>○ Cystitis</li> <li>○ Other Sepsis</li> <li>○ Mycoplasma pneumoniae</li> <li>○ Cellulitis</li> <li>○ Streptococcal pharyngitis</li> <li>○ Drugs and other substances, not normally found in the blood</li> <li>○ Cutaneous abscess</li> <li>○ Symptoms and signs specifically associated with systemic inflammation and infection</li> <li>○ Streptococcus, staphylococcus and enterococcus</li> <li>○ Local infections of the skin and subcutaneous tissue</li> <li>○ Otitis externa</li> <li>○ Osteomyelitis</li> </ul> </li> </ul>	209 28 55 15 5 39 18 30 20 94 759  113 72 49 37 18 17 17 16 16 15 13 12	17.3% 2.3% 4.5% 1.2% 0.4% 3.2% 1.5% 2.5% 1.7% 7.8% 62.8%  9.3% 6.0% 4.1% 3.1% 1.5% 1.4% 1.4% 1.3% 1.3% 1.2% 1.1% 1.0%

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

Medical claims for an adverse event identified by the FDA to be associated with FQ use occurred in about 36% of patients taking either ciprofloxacin or levofloxacin. Joint pain was the most common adverse event for ciprofloxacin (27.0%) and levofloxacin (33.2%) (Table 3). The second most common adverse events were related to mental health diagnoses, which was more common with levofloxacin (5.6%) compared to ciprofloxacin (3.8%). A similar number of patients had one of these identified adverse events in the 6 months before the FQ reference claim (19.4%) and the 6 months after the claim (21.3%), which weakens the correlation of an adverse events with FQ use (Table 4).

**Table 3. Fluoroquinolone Adverse Events\***

	Ciprofloxacin		Levofloxacin	
	Claims	Patients	Claims	Patients
<b>Adverse Event Type</b>				
Hypoglycemia (ICD-10: E09.64x, E10.64x, E11.64x, E13.64x, E16.0-E16.2)	47	20 (2.4%)	35	9 (2.4%)
Mental health concerns: (ICD-10: [disorientation] R41.0, [nervousness] R45.0, [restlessness] R45.1, [mild cognitive impairment] G31.84, [delirium] F05)	53	32 (3.8%)	33	21 (5.6%)
Tendonitis (ICD-10: M65.2x, M75.2x, M75.3, M76.0x, M76.1x, M76.5x, M76.6x, M76.7x, M76.82x)	18	10 (1.2%)	11	4 (1.1%)
Joint pain (ICD-10: M25.5x)	581	226 (27.0%)	314	124 (33.2%)
Death	4	4 (0.5%)	3	3 (0.8%)
Total number of Adverse Event Claims	258	258 (30.9%)	134	134 (35.9%)

\* Combination of those occurring 6 months before or after the reference claim

**Table 4. Incidence of adverse events in relation to FQ claims**

	Patients (n=1209)	Claims
Adverse event up to 6 months after the FQ reference claim	258 (21.3%)	570
Adverse event up to 6 months before the reference claim	235 (19.4%)	508
Adverse events which occurred both before and after FQ use (up to 6 months before and up to 6 months after the reference claim)	101 (8.4%)	528

As previously mentioned, the number of patients with an adverse event and FQ claim was around 32%, with the majority of claims for an unidentified diagnosis (62.8%) (Table 5). Only 12.9% of patients were hospitalized within the previous 30 days and almost 85% of patients had no prior antibiotic claim within 30 days of the FQ reference claim, inferring that the FQ was most likely prescribed as a first-line antibiotic. Hospitalizations 30 days after the reference claim were 3.7% (Table 5). This was substantiated by a low incidence of antibiotic allergy diagnoses (8.6%) in patients with a FQ claim. Twenty seven percent (n=320) of patients did have a comorbidity that could increase the risk for an adverse event and there was a 50% adverse event occurrence rate in patients with a comorbidity (162/320). Most of the prescribers of FQ antibiotics were family medicine or internal medicine physicians, nurse practitioners, or physician assistants (Table 6).

Claims prescribed by emergency medicine physicians were also among the top prescribers of FQ (14.7%) (Table 6). Sixty-five percent of patients were prescribed one to two week supplies of FQ. Subsequent use of a FQ was low, around 1-1.7% (Table 7).

**Table 5. Summary of Fluoroquinolone Utilization**

	Number	Percent
Patients with FQ claim in 2018	1,209	
Person with adverse events identified by the FDA as associated with FQ	392	32.4%
No prior antibiotic use with in previous 30 days	1,025	84.8%
Patients with hospital discharge in 30 days prior to reference claim	156	12.9%
Patients with hospital discharge in 30 days after reference claim	45	3.7%
Prior antibiotic use within previous 30 days of reference claim	184	15.2%
Patients with a diagnosis for an antibiotic allergy in prior 2 years	104	8.6%
<ul style="list-style-type: none"> <li>Patients with a diagnosis for an antibiotic allergy in prior 2 years with no prior antibiotic use in the previous 30 days</li> </ul>	89	7.4%
Patients with a comorbidity listed above	320	26.5%
Patients with a comorbidity and adverse events identified by the FDA as associated with FQ	162	13.4%
Abbreviations: FQ – fluoroquinolone		

**Table 6. Common prescriber types for the reference claim**

Prescriber Type	Number of Patients	Percent
Physician-Family Medicine	247	20.4%
Nurse Practitioner-Family	205	17.0%
Physician-Emergency Medicine	178	14.7%
Physician Assistant	103	8.5%
Physician-Internal Medicine	100	8.3%
Physician Assistant-Medical	51	4.2%
Physician-Hospitalist	48	4.0%

**Table 7. Fluoroquinolone Days Supply**

Days' Supply	Days' Supply for the Reference Claim	Days' supply in the 30 days after the reference claim
<3 days	29 (2.4%)	1 (0.1%)
3-5 days	354 (29.3%)	21 (1.7%)
6-7 days	425 (35.2%)	12 (1.0%)
8-14 days	367 (30.4%)	13 (1.1%)
>14 days	34 (2.8%)	15 (1.2%)

## Limitations:

Inherent limitations to Medicaid claims data:

- Accuracy of diagnosis: Diagnoses data based on claims may be inaccurate or incomplete. Diagnoses are not associated with prescription claims, therefore it is difficult to determine the intended indication of the drug. Additionally, there is a large number of patients who received a FQ without an identified diagnosis, limiting the ability to determine appropriate use.
- Provider Specialty: Information on provider specialty may be inaccurate, out-of-date, or incomplete for some providers. Prescribers with multiple specialties or designation may not be identified.
- Days of coverage: Estimated number of covered days attempts to approximate days of total antibiotic use given the frequency which a typical patient takes a prescription. But accuracy of this method has not been validated, as covered days may not accurately correlate to actual medication adherence, and patients may not always be categorized appropriately.
- Correlation of adverse events: There is no way to determine if the adverse event identified via claims was definitively associated with FQ use.
- Prior antibiotic use: It is unknown if the patient received a previous antibiotic as a sample, paid cash or has a history of intolerance to first-line therapies.
- Antibiotic Allergy: Failure to document an antibiotic allergy could potentially lead to misinterpretation of appropriate first-line antibiotic use.

## References:

1. Food and Drug Administration. FDA advises restricting FQ antibiotic use for certain uncomplicated infections; warns about disabling side effects that can occur together. FDA Drug Safety Communication. 12 May 2016. Available at: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-advises-restricting-fluoroquinolone-antibiotic-use-certain>. Accessed 5 November 2019.
2. Food and Drug Administration. FDA updates warnings for oral and injectable fluoroquinolone antibiotics due to disabling side effects. FDA Drug Safety Communications. 26 July 2016. Available at: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-updates-warnings-oral-and-injectable-fluoroquinolone-antibiotics>. Accessed 5 November 2019.
3. Food and Drug Administration. FDA reinforces safety information about serious low blood sugar levels and mental health side effects with fluoroquinolone antibiotics; requires label changes. Available at: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-reinforces-safety-information-about-serious-low-blood-sugar-levels-and-mental-health-side>. Accessed 5 November 2019.
4. Food and Drug Administration. FDA warns about increased risk of ruptures or tears in the aorta blood vessel with fluoroquinolone antibiotics in certain patients. FDA Drug Safety Communications. 20 December 2018. Available at: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-increased-risk-ruptures-or-tears-aorta-blood-vessel-fluoroquinolone-antibiotics>. Accessed 5 November 2019.

## Appendix 1: Search Strategy

1. FDA boxed warnings from 1/01/2015 – 11/14/2019
2. FDA drug safety communications 1/01/2015 – 11/14/2019

## Appendix 2. Drug Coding

Table A1. Other potentially relevant infectious diagnoses associated with patients who had a FQ claim

<u>ICD-10</u> <u>code</u>	<u>Description</u>		
A020	Salmonella enteritis	A021	Salmonella sepsis
		A030	Shigellosis due to Shigella dysenteriae
		A0472	Enterocolitis d/t Clostridium difficile, not spcf as recur

A09	Infectious gastroenteritis and colitis, unspecified	H6001	Abscess of right external ear
A310	Pulmonary mycobacterial infection	H6022	Malignant otitis externa, left ear
A403	Sepsis due to Streptococcus pneumoniae	H60311	Diffuse otitis externa, right ear
A4101	Sepsis due to Methicillin susceptible Staphylococcus aureus	H60312	Diffuse otitis externa, left ear
A4102	Sepsis due to Methicillin resistant Staphylococcus aureus	H60313	Diffuse otitis externa, bilateral
A412	Sepsis due to unspecified staphylococcus	H60333	Swimmer's ear, bilateral
A413	Sepsis due to Hemophilus influenzae	H60392	Other infective otitis externa, left ear
A4150	Gram-negative sepsis, unspecified	H60501	Unspecified acute noninfective otitis externa, right ear
A4151	Sepsis due to Escherichia coli [E. coli]	H60502	Unspecified acute noninfective otitis externa, left ear
A4153	Sepsis due to Serratia	H60503	Unspecified acute noninfective otitis externa, bilateral
A4159	Other Gram-negative sepsis	H6063	Unspecified chronic otitis externa, bilateral
A4189	Other specified sepsis	H6091	Unspecified otitis externa, right ear
A419	Sepsis, unspecified organism	H6092	Unspecified otitis externa, left ear
A480	Gas gangrene	H6501	Acute serous otitis media, right ear
A4901	Methicillin suscep staph infection, unsp site	H6503	Acute serous otitis media, bilateral
A4902	Methicillin resis staph infection, unsp site	H65119	Acute and subacute allergic otitis media (serous), unsp ear
A499	Bacterial infection, unspecified	H6590	Unspecified nonsuppurative otitis media, unspecified ear
A5601	Chlamydial cystitis and urethritis	H6591	Unspecified nonsuppurative otitis media, right ear
A749	Chlamydial infection, unspecified	H6593	Unspecified nonsuppurative otitis media, bilateral
B951	Streptococcus, group B, causing diseases classd elswhr	I2690	Septic pulmonary embolism without acute cor pulmonale
B952	Enterococcus as the cause of diseases classified elsewhere	I330	Acute and subacute infective endocarditis
B955	Unsp streptococcus as the cause of diseases classd elswhr	I38	Endocarditis, valve unspecified
B9561	Methicillin suscep staph infct causing dis classd elswhr	I96	Gangrene, not elsewhere classified
B9562	Methicillin resis staph infct causing diseases classd elswhr	J020	Streptococcal pharyngitis
B957	Oth staphylococcus as the cause of diseases classd elswhr	J028	Acute pharyngitis due to other specified organisms
B958	Unsp staphylococcus as the cause of diseases classd elswhr	J029	Acute pharyngitis, unspecified
B9620	Unsp Escherichia coli as the cause of diseases classd elswhr	J851	Abscess of lung with pneumonia
B9629	Oth Escherichia coli as the cause of diseases classd elswhr	J852	Abscess of lung without pneumonia
B964	Proteus (mirabilis) (morganii) causing dis classd elswhr	K5100	Ulcerative (chronic) pancolitis without complications
B965	Pseudomonas (mallei) causing diseases classd elswhr	K51011	Ulcerative (chronic) pancolitis with rectal bleeding
B9681	Helicobacter pylori as the cause of diseases classd elswhr	K51013	Ulcerative (chronic) pancolitis with fistula
B9689	Oth bacterial agents as the cause of diseases classd elswhr	K51018	Ulcerative (chronic) pancolitis with other complication
D61810	Antineoplastic chemotherapy induced pancytopenia	K5180	Other ulcerative colitis without complications
D61818	Other pancytopenia	K51811	Other ulcerative colitis with rectal bleeding
D701	Agranulocytosis secondary to cancer chemotherapy	K5190	Ulcerative colitis, unspecified, without complications
D709	Neutropenia, unspecified	K521	Toxic gastroenteritis and colitis
D72819	Decreased white blood cell count, unspecified	K523	Indeterminate colitis
E849	Cystic fibrosis, unspecified	K652	Spontaneous bacterial peritonitis
G039	Meningitis, unspecified	L0201	Cutaneous abscess of face
		L02214	Cutaneous abscess of groin

L02219	Cutaneous abscess of trunk, unspecified	M86479	Chronic osteomyelitis w draining sinus, unsp ankle and foot
L02411	Cutaneous abscess of right axilla	M86642	Other chronic osteomyelitis, left hand
L02415	Cutaneous abscess of right lower limb	M86671	Other chronic osteomyelitis, right ankle and foot
L02416	Cutaneous abscess of left lower limb	M86672	Other chronic osteomyelitis, left ankle and foot
L02511	Cutaneous abscess of right hand	M8668	Other chronic osteomyelitis, other site
L02611	Cutaneous abscess of right foot	M868X7	Other osteomyelitis, ankle and foot
L02612	Cutaneous abscess of left foot	M869	Osteomyelitis, unspecified
L02619	Cutaneous abscess of unspecified foot	N3000	Acute cystitis without hematuria
L02811	Cutaneous abscess of head [any part, except face]	N3001	Acute cystitis with hematuria
L0291	Cutaneous abscess, unspecified	N3010	Interstitial cystitis (chronic) without hematuria
L03011	Cellulitis of right finger	N3020	Other chronic cystitis without hematuria
L03031	Cellulitis of right toe	N3081	Other cystitis with hematuria
L03032	Cellulitis of left toe	N3090	Cystitis, unspecified without hematuria
L03112	Cellulitis of left axilla	N3091	Cystitis, unspecified with hematuria
L03114	Cellulitis of left upper limb	N410	Acute prostatitis
L03115	Cellulitis of right lower limb	N730	Acute parametritis and pelvic cellulitis
L03116	Cellulitis of left lower limb	N736	Female pelvic peritoneal adhesions (postinfective)
L03119	Cellulitis of unspecified part of limb	N739	Female pelvic inflammatory disease, unspecified
L03211	Cellulitis of face	R6520	Severe sepsis without septic shock
L03311	Cellulitis of abdominal wall	R6521	Severe sepsis with septic shock
L03313	Cellulitis of chest wall	R7881	Bacteremia
L03314	Cellulitis of groin	R8271	Bacteriuria
L03319	Cellulitis of trunk, unspecified	T80218A	Other infection due to central venous catheter, init encntr
L0390	Cellulitis, unspecified	T8142XA	Infct fol a procedure, deep incisional surgical site, init
L0889	Oth local infections of the skin and subcutaneous tissue	T814XXA	Infection following a procedure, initial encounter
L089	Local infection of the skin and subcutaneous tissue, unsp	T814XXD	Infection following a procedure, subsequent encounter
M00041	Staphylococcal arthritis, right hand	T826XXA	Infect/inflm reaction due to cardiac valve prosthesis, init
M00061	Staphylococcal arthritis, right knee	T826XXS	Infect/inflm reaction due to cardiac valve prosth, sequela
M00062	Staphylococcal arthritis, left knee	T827XXA	Infect/inflm react d/t oth cardi/vasc dev/implnt/grft, init
M86072	Acute hematogenous osteomyelitis, left ankle and foot	T83510A	I/I react d/t cystostomy catheter, initial encounter
M8608	Acute hematogenous osteomyelitis, other sites	T83511A	I/I react d/t indwelling urethral catheter, init
M86171	Other acute osteomyelitis, right ankle and foot	T8459XA	Infect/inflm reaction due to oth internal joint prosth, init
M86172	Other acute osteomyelitis, left ankle and foot	T8579XS	Infect/inflm react due to oth int prosth dev/grft, sequela
M86371	Chronic multifocal osteomyelitis, right ankle and foot	Z5111	Encounter for antineoplastic chemotherapy
M86372	Chronic multifocal osteomyelitis, left ankle and foot	Z5112	Encounter for antineoplastic immunotherapy
M86472	Chronic osteomyelitis w draining sinus, left ankle and foot		

## Drug Class Literature Scan: Diuretics

**Date of Review:** June 2020

**Date of Last Review:** November 2014  
**Literature Search:** 09/01/14 – 11/22/19

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

### Conclusions:

- Seven clinical practice guidelines<sup>1-7</sup>, 17 systematic reviews<sup>8-24</sup>, and 2 randomized controlled trials (RCTs)<sup>25,26</sup> identified for this update.
- Thiazide-type diuretics are recommended as a first-line treatment option for hypertension. High-dose diuretic regimens have been shown to reduce mortality and stroke (moderate quality evidence), while low-dose regimens have been found to reduce mortality, stroke, coronary heart disease, and total cardiovascular events (high quality evidence). Evidence for use of “low” dose thiazide-type diuretics is stronger than “high” dose thiazide-type diuretics.<sup>1-4,10,12</sup> Low doses are less than chlorthalidone (CTDN) 50 mg per day, indapamide (INDAP) 5 mg per day or hydrochlorothiazide (HCTZ) 50 mg per day.<sup>10</sup> High doses are CTDN 50 mg or more each day, INDAP 5 mg more each day, or HCTZ 50 mg or more each day.<sup>10</sup>
- Thiazide-like diuretics [e.g. CTDN and INDAP] are preferred over thiazide diuretics [e.g HCTZ] by certain high quality guidelines,<sup>1-3</sup> while another guideline has no preference between the two agent types.<sup>4</sup> These recommendations were all based on the same body of literature. High quality RCTs of CTDN and INDAP show cardiovascular benefits as well as pharmacokinetic superiority in the form prolonged half-life compared to HCTZ, but there is insufficient evidence to *directly* compare these agents for efficacy and safety.<sup>1-4,18,27</sup>
- Loop diuretics are recommended for edema in heart failure (HF) but they have not been shown to reduce mortality, and there is insufficient evidence to differentiate between agents.<sup>5-7,19,28</sup> (low quality evidence)
- Mineralocorticoid receptor antagonists (MRA) are recommended to reduce mortality in most patients with HF with reduced ejection (HF<sub>r</sub>EF) who already take an angiotensin-converting enzyme inhibitor (ACEI)/angiotensin II receptor blocker (ARB) and a beta blocker (BB).<sup>5-7</sup> (High quality evidence)
- MRAs (e.g. spironolactone and eplerenone) have limited evidence that they improve protein/creatinine ratio in diabetic nephropathy (DN) when used in combination with an ACEI or ARB. Hyperkalemia incidence increases with this combination.<sup>24</sup>
- MRA use in HF with preserved ejection fraction (HF<sub>p</sub>EF) and HF with moderately reduced ejection fraction (HF<sub>mr</sub>EF) may reduce hospitalizations. There is possible mortality benefit for those patients who are also status post ST-elevation myocardial infarction (STEMI).<sup>6,7,20-22</sup> (low quality evidence)
- Spironolactone has evidence to support its use in resistant hypertension, with appropriate monitoring due to higher incidence of hyperkalemia.<sup>1,2,14,15,17</sup> (moderate quality evidence)
- The effect of thiazide-type diuretics on glucose metabolism, particularly HCTZ, is unclear.<sup>23</sup> (insufficient quality evidence)
- There is insufficient data to differentiate between different MRA medications.<sup>5-7</sup> (insufficient quality evidence)
- There is insufficient evidence for the use of loop diuretics for blood pressure reduction.<sup>9</sup> (insufficient quality evidence)
- There is insufficient evidence to make recommendations regarding diuretic use in children.<sup>8</sup> (insufficient quality evidence)

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**Recommendations:**

- Add CTDN to the OHP FFS preferred drug list (PDL).
- No further recommendations based on clinical data. Evaluate comparative drug costs in the executive session.

**Summary of Prior Reviews and Current Policy**

- High quality evidence suggests thiazide-type diuretics should continue to be recommended as a first-line option for hypertension due to benefit at reducing mortality and stroke.
- Thiazide-type diuretics with high quality data include HCTZ, CTDN and INDAP.
- There is insufficient evidence demonstrating efficacy and safety differences among different thiazide diuretics. Hydrochlorothiazide is the only thiazide diuretic with evidence of dose-dependent lowering of blood pressure (BP).
- There is high quality evidence loop diuretics provide short-term relief of fluid retention in symptomatic heart failure patients with preserved or reduced left ventricular ejection fraction (LVEF). However, there is insufficient evidence to confirm long term benefits of diuretics in patients with heart failure.
- There is insufficient evidence comparing efficacy and safety differences among different loop diuretics.
- There is high quality evidence that aldosterone receptor antagonists (spironolactone or eplerenone), unless contraindicated, reduce morbidity and mortality when added to evidence-based heart failure therapy in patients with systolic heart failure and reduced LVEF. There is insufficient evidence comparing spironolactone with eplerenone.
- There is moderate quality evidence that adding spironolactone to patients with systolic heart failure and preserved LVEF reduces hospitalizations; however, spironolactone does not yield any additional morbidity or mortality benefit.

**Background:**

The diuretics class encompasses multiple sub-classes of agents which differ mechanistically.<sup>29</sup> The most familiar agents are loop diuretics, thiazide-type diuretics, and potassium-sparing diuretics.<sup>29</sup> Potassium sparing diuretics are divided into agents which directly block sodium channels without antagonism of mineralocorticoid receptor (e.g., amiloride) and agents which function with direct inhibition of the mineralocorticoid receptor (e.g., spironolactone).<sup>29</sup> Additionally, there are a number of miscellaneous medications such as carbonic anhydrase inhibitors, osmotic diuretics, or vasopressin antagonists which function with diuretic properties; however, their clinical use varies significantly from disease states commonly treated with loop, thiazide-type, and potassium sparing agents.<sup>29</sup> These miscellaneous agents were excluded for the purpose of this review.

Loop, thiazide-type, and potassium-sparing diuretics are most commonly used for hypertension and heart failure.<sup>1,6</sup> Elevated blood pressure increases risk of complications such as myocardial infarction, stroke, heart failure, and kidney disease.<sup>1</sup> It was the leading cause of death and disability-adjusted life years worldwide in 2010.<sup>1</sup> Hypertension has been the cause of more cardiovascular deaths than any other modifiable risk factor.<sup>1</sup> Risk for developing hypertension increases with age and is more common in African-Americans than other races.<sup>1</sup> Diuretics, with thiazide-type agents being used most commonly for hypertension, work by causing a net excretion of water, resulting in decreased blood pressure.<sup>29</sup> Depending upon comorbidities and electrolyte levels, different diuretic sub-types can be combined<sup>1</sup>, though combinations require close monitoring to avoid adverse effects such as electrolyte abnormalities, dehydration, and acute kidney injury.<sup>29</sup>

Heart failure is a clinical syndrome involving structural or functional impairment of ventricular filling or ejection of blood.<sup>28</sup> It primarily manifests with symptoms of dyspnea, fatigue, and fluid retention.<sup>28</sup> There is a 20% lifetime risk for development of heart failure in Americans 40 years of age and older, and risk increases

with increasing age.<sup>28</sup> Diuretics, primarily loop agents, find utility in reducing symptoms of fluid overload in heart failure.<sup>28</sup> Potassium-sparing agents with mineralocorticoid inhibition have also been shown to improve outcomes,<sup>28</sup> likely due to a reduction of the adverse effects of excess aldosterone on the heart.<sup>29</sup>

### **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.

### **Systematic Reviews:**

After review, 26 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).<sup>27,30-54</sup>

### **New Systematic Reviews on Hypertension:**

#### Cochrane Review-Pharmacological Interventions for Hypertension in Children

A 2014 *Cochrane Review* assessed antihypertensive agents in children with hypertension.<sup>8</sup> Randomized controlled trials using mono- or combination therapy and an active or placebo control of at least two weeks duration were included.<sup>8</sup> None of the included trials assessed effectiveness of medications on target end organ damage, and only one study evaluated use of a diuretic (bisoprolol plus HCTZ versus placebo; n=94).<sup>8</sup> This study did not show a significant systolic BP (SBP) reduction versus placebo [mean difference -4 mmHg, 95% confidence Interval [CI] -8.99 to 0.19 mmHg].<sup>8</sup> It did report a significant reduction of diastolic BP (DBP) [-4.5 mmHg, 95% CI -8.26 to -0.74 mmHg].<sup>8</sup> Outcomes were graded as very low quality.<sup>8</sup>

#### Cochrane Review-Blood Pressure-Lowering Efficacy of Loop Diuretics for Primary Hypertension

A 2015 *Cochrane Review* assessed the dose-dependent BP-lowering effects of loop diuretics versus placebo in patients with primary hypertension.<sup>9</sup> Additionally, adverse events such as participant withdrawal and adverse biochemical effects (serum potassium, uric acid, creatinine, glucose, and lipids profile) were assessed.<sup>9</sup> Double-blind, placebo-controlled RCTs with a minimum of 3-weeks duration that studied loop diuretics for primary hypertension in patients with baseline BP of more than 140/90 mmHg were included.<sup>9</sup> Nine studies evaluating furosemide, cicletanone, piretanide, indacrinone enantiomer, or etozolin met inclusion criteria (n=460).<sup>9</sup> Furosemide is the only included product available in the US. Patients in the included studies had an average baseline BP of 162/103 mmHg and were treated with loop diuretics for a mean duration of 8.8 weeks. The estimated SBP-lowering effect for loop diuretics was -7.9 mmHg (95% CI -10.4 to -5.4 mmHg) and DBP-lowering was -4.4 mmHg (95% CI -5.9 to -2.8 mmHg). Evidence was of low quality based on high risk of bias in included studies and high likelihood of publication bias.<sup>9</sup> There was minimal reporting of adverse drug effects and the studies were of short duration, making the review unable to estimate incidence of harm associated with loop diuretic use for primary hypertension.<sup>9</sup>

### Cochrane Review-Pharmacotherapy for Hypertension in Adults Aged 18 to 59 Years

A 2017 *Cochrane Review* assessed antihypertensive drug therapy in adults to quantify all-cause mortality and morbidity and mortality secondary to cardiovascular, cerebrovascular, and coronary heart disease (CHD).<sup>11</sup> Reviewers included placebo-controlled RCTs in adult patients aged 18-59 years with mild-to-moderate hypertension (defined as SBP  $\geq$  140 mmHg and/or DBP  $\geq$  90 mmHg) for a least one year duration.<sup>11</sup> The overall quality of evidence for all outcomes was rated as low to very low, and risk of bias was high or unclear in multiple domains.<sup>11</sup> Seven studies (N=17,327) met inclusion criteria, and of these one study included 84% (N=14,541) of the total participants.<sup>11</sup> Patients in this study had a mean age of 50 years, mean baseline BP of 160/98 mmHg, and mean follow-up of 5 years.<sup>11</sup> The medication intervention in the primary study was bendrofluzide (not available in US) or propranolol with the addition of methyldopa if needed.<sup>11</sup> There was no difference observed in all-cause mortality [relative risk (RR) 0.94, 95% CI 0.77 to 1.13] or CHD (RR 0.99, 95% CI 0.82 to 1.19).<sup>11</sup> Cardiovascular mortality and morbidity (fatal and non-fatal stroke, fatal and non-fatal myocardial infarction, sudden death, hospitalization or death from congestive heart failure or other significant vascular death such as ruptured aneurysms) was reduced over a period of 5 years (3.2% treatment vs. 4.1% active control; RR 0.78, 95% CI 0.67 to 0.91), in part driven by a reduction in cerebrovascular mortality and morbidity (0.6% treatment vs. 1.3% control; RR 0.46, 95% CI 0.34 to 0.64).<sup>11</sup> There was a higher rate of withdrawals from adverse events for those taking drug therapy when compared to placebo or untreated controls (3% treatment vs. 0.7% control; RR 4.82, 95% CI 1.67 to 13.92).<sup>11</sup>

### Cochrane Review-Eplerenone for Hypertension

A 2017 *Cochrane Review* assessed evidence from placebo-controlled RCTs of eplerenone monotherapy for primary hypertension in adults.<sup>13</sup> Trials evaluating secondary hypertension or which used multiple antihypertensives were excluded.<sup>13</sup> This review identified 5 RCTs (n = 1,437 patients) with treatment durations of 8 to 16 weeks and eplerenone doses ranging from 25 mg to 400 mg daily.<sup>13</sup> There was moderate quality evidence of a significant change in SBP (-9.21 mmHg, 95% CI -11.08 to -7.34 mmHg) and DBP (-4.18 mmHg, 95% CI -5.03 to -3.33 mmHg) for eplerenone doses of 50 mg to 200 mg each day.<sup>13</sup> The studies had an unclear risk of bias in multiple domains, including: sequence generation; blinding of participants, personnel, and assessors; incomplete outcome data; and selective outcome reporting.<sup>13</sup> All were unclear or had other known sources of bias.<sup>13</sup> Adverse events were recorded in only 3 of 5 studies and evidence was of low quality.<sup>13</sup> There was insufficient evidence on clinically meaningful outcomes of morbidity and mortality.<sup>13</sup>

### Cochrane Review-First-line Drugs for Hypertension

A 2018 *Cochrane Review* assessed the use of different first-line antihypertensive classes and their effect on morbidity and mortality.<sup>10</sup> The authors included thiazide diuretics, BB, calcium channel blockers (CCB), ACEI, ARB, and alpha blockers compared to placebo or no treatment.<sup>10</sup> This update from a 2009 review included RCTs of at least 1 year duration, comparing these drugs to placebo or no treatment with clearly defined morbidity and mortality endpoints and analysis using intention-to-treat (ITT).<sup>10</sup> No additional citations met inclusion criteria since the initial search in 2009.<sup>10</sup> Results for individual thiazide agents were not separately evaluated, and were presented as “low-dose” and “high-dose” subgroups.<sup>10</sup> Low doses are less than CTDN 50 mg per day, INDAP 5 mg per day or HCTZ 50 mg per day.<sup>10</sup> High doses are CTDN 50 mg or more each day, INDAP 5 mg or more each day, or HCTZ 50 mg or more each day.<sup>10</sup> Low-dose thiazides had high quality evidence, while high-dose thiazides were of low-moderate quality evidence.<sup>10</sup> Low-dose thiazides significantly reduced mortality (9.8% treatment vs. 11% control; RR 0.89, 95% CI 0.82 to 0.97; N=19,874), stroke (4.2% treatment vs. 6.2% control; RR 0.68, 95% CI 0.6 to 0.77; N=19,874), CHD (2.8% treatment vs. 3.9% control; RR 0.72, 95% CI 0.61 to 0.84; N=19,022) and total cardiovascular events (9% treatment vs. 12.9% control; RR 0.7, 95% CI 0.64 to 0.76; N=19,022).<sup>10</sup> High-dose thiazides did not significantly reduce mortality or CHD, but did reduce stroke (0.9% treatment vs. 1.9% control; RR 0.47, 95% CI 0.37 to 0.61; N=19,839) and total cardiovascular events (3.7% treatment vs. 5.1% control; RR 0.72, 95% CI 0.63 to 0.82; N=19,839).<sup>10</sup>

## Cochrane Review-Pharmacotherapy for Hypertension in Adults 60 Years or Older

A 2019 Cochrane review updated previous publications from 1998 and 2009 to assess the mortality and morbidity associated with antihypertensive treatment versus placebo or no treatment for patients 60 years and older with BP over 140/90 mmHg.<sup>12</sup> This update included one additional trial for a total of 16 trials (N=26,795).<sup>12</sup> The mean age was 73.4 years, baseline BP was 182/95 mmHg, and thiazide diuretics were the most common first-line therapy.<sup>12</sup> Patients were followed for a mean duration of 3.8 years and were primarily from western, industrialized countries.<sup>12</sup> Treatment reduced all-cause mortality (10% treatment vs. 11% control; RR 0.91, 95% CI 0.85 to 0.97) with high quality evidence.<sup>12</sup> Cardiovascular morbidity and mortality (9.8% treatment vs. 13.6% control; RR 0.72, 95% CI 0.68 to 0.77), cerebrovascular morbidity and mortality (3.4% treatment vs. 5.2% control; RR 0.66, 95% CI 0.59 to 0.74), and CHD morbidity and mortality (3.7% treatment vs. 4.8% control; RR 0.78; 95% CI 0.69 to 0.88) were all reduced based on moderate quality evidence.<sup>12</sup> Additionally, an analysis of patients aged 60-79 years provide high quality evidence that much of the overall benefit for those over 60 years of age is derived from the all-cause mortality reduction in this subgroup (2.9% treatment vs. 3.8 % control; RR 0.86, 95% CI 0.79 to 0.95).<sup>12</sup> Adverse effects resulting in withdrawal from studies were higher in treatment groups (15.7% treatment vs. 5.4% control; RR 2.91, 95% CI 2.56 to 3.3) based on low quality evidence.<sup>12</sup>

## Treatment-Resistant Hypertension

Four systematic reviews of moderate quality evaluated spironolactone for resistant hypertension, defined as uncontrolled BP while on optimal doses of 3 or more antihypertensive agents from different pharmacological classes.<sup>14-17</sup> Significant overlap of source trials existed in the included analyses, as well as marked variation of the results of the risk of bias assessment for identical included trials.<sup>14-17</sup> Authors of all these systematic reviews noted significant heterogeneity among included studies. Average reduction in SBP was estimated at 8 to 10 mmHg with average reductions in DBP of 4 to 5 mmHg. In one review, rates of withdrawals and serious adverse events, usually hyperkalemia, were non-significantly higher in spironolactone-treated patients (OR 2.11, 95% CI 0.98 to 4.53, p=0.05). In another review, mean serum potassium increases of 0.181 mEq/L (95% CI 0.042 to 0.319 mEq/L, p=0.011) were observed.

## Comparison of Diuretics for Hypertension

A moderate quality systematic review with meta-analysis evaluated head-to-head trials of HCTZ versus thiazide-like diuretics (INDAP or CTDN).<sup>18</sup> There were 12 included studies (n=1,580 patients) which ranged from 4 to 24 weeks in duration.<sup>18</sup> Compared to HCTZ, thiazide-like diuretics had a greater reduction in SBP (-5.59 mmHg, 95% CI -5.69 to -5.49 mmHg, p<0.00001) and DBP (-1.98 mmHg, 95% CI -3.29 to -0.66 mmHg, p<0.00001).<sup>18</sup> Heterogeneity was low in the SBP calculation (I<sup>2</sup>=10%), but high in the DBP calculation (I<sup>2</sup>=85%).<sup>18</sup> Analysis of serum markers showed no between-group differences in hypokalemia (OR 1.58, 95% CI 0.8 to 3.12, p=0.16), hyponatremia [standard mean difference (SMD) -0.14, 95% CI -0.57 to 0.3, p=0.71], total cholesterol (0.11, 95% CI -0.02 to 0.24, p=0.11), or glucose (0.13, 95% CI -0.16 to 0.41, p=0.39).<sup>18</sup> Significant heterogeneity was present for the glucose calculation only (I<sup>2</sup>=69%).<sup>18</sup>

## Metabolic and Renal Outcomes in Diabetic Patients

The adverse metabolic effects of HCTZ were assessed in patients with hypertension and type 2 diabetes mellitus (T2DM).<sup>23</sup> This review included studies of 4 to 144 weeks duration in patients taking an active control of a BB, CCB, ACEI, or ARB and found a statistically significant increase in fasting glucose (SMD 0.27, 95% CI 0.11 to 0.43, p<0.05) and HbA1C (SMD 1.09, 95% CI 0.47 to 1.71, p<0.05) for patients in the HCTZ-treated group versus active controls.<sup>23</sup> Results were consistent even in patients treated with a low dose HCTZ of 25 mg per day or less.<sup>23</sup>

The effect of MRA was evaluated in a systematic review of patients with diabetic nephropathy.<sup>24</sup> Eligible studies evaluated spironolactone (n=13), eplerenone (n=2), and finerenone (n=2; not available in US).<sup>24</sup> The protein/albumin excretion was significantly reduced with the addition of a MRA to ACEI/ARB therapy versus ACEI/ARB monotherapy [mean difference (MD) -44.17 mg/24 hours, 95% CI -61.73 to -26.61 mg/24 hours, p<0.00001].<sup>24</sup> There was a significant increase in serum

potassium with addition of an MRA (MD 0.27 mEq/L, 95% CI 0.18 to 0.35 mEq/L,  $p < 0.00001$ ) and increased risk of hyperkalemia (RR 4.02, 95% CI 2.48 to 6.52,  $p < 0.00001$ ).<sup>24</sup>

## **New Systematic Reviews on Heart Failure:**

### Moderate Quality Systematic Reviews on Diuretic use in Heart Failure (HF)

Three separate meta-analyses evaluated the use of MRAs in patients with HFpEF.<sup>20-22</sup> Dahal, et al. focused on patients post-STEMI without HF or with LVEF greater than 40%. The review included 10 studies, with oral MRA (spironolactone, potassium canrenoate, eplerenone) or intravenous (IV) potassium canrenoate followed by oral spironolactone or potassium canrenoate compared to placebo or no treatment.<sup>20</sup> One study included eplerenone.<sup>20</sup> The authors found an overall reduction in the risk of mortality with MRA use versus control (2.4% vs 3.9%; OR 0.62; 95% CI 0.42-0.91,  $p = 0.01$ ). No difference between the groups were found in the incidence of MI, congestive heart failure, or ventricular arrhythmia.<sup>20</sup>

A second meta-analysis of RCTs for patients with HFpEF (defined as EF  $\geq 45\%$ ) identified two studies related to all-cause mortality and hospitalization taking spironolactone or placebo.<sup>21</sup> No reduction in all-cause mortality (OR 0.91; 95% CI 0.76-1.1;  $p = 0.32$ ) or hospitalization rates (OR 1.0; 95% CI 0.8-1.25;  $p = 1.00$ ) was found.<sup>21</sup> Similarly, a meta-analysis of RCTs enrolling HFpEF (EF  $> 50\%$ ) and HFmrEF (EF = 40-49%) found no difference in mortality between patients taking spironolactone versus placebo (RR 0.72; 95% CI 0.31-1.69;  $p = 0.45$ ;  $n = 3$  RCTs).<sup>22</sup> However, 2 pooled studies showed spironolactone decreased hospital readmissions (OR 0.84; 95% CI 0.73-0.95;  $p = 0.006$ ).<sup>22</sup>

The third meta-analysis evaluated ambulatory heart failure patients (primarily NYHA class II-III) on torsemide or furosemide for 5 to 12 months.<sup>19</sup> There was no difference in all-cause mortality (OR 1.01, 95% CI 0.64-1.59).<sup>19</sup> Patients taking furosemide showed higher risk of heart failure related readmission (OR 2.16, 95% CI 1.28-2.64). Those taking torsemide were more likely to have NYHA class improvement during the follow-up time range (OR 0.73, 95% CI 0.58-0.93).<sup>19</sup>

## **New Guidelines:**

### Hypertension

#### National Institute for Health and Care Excellence (NICE)

In 2019, NICE published guidelines for the diagnosis and management of hypertension in non-pregnant adults, including those with T2DM.<sup>2</sup> Treatment is recommended in stepwise fashion, and is based on various age, race, and comorbidity factors. For step 1 therapy, initiation of an ACEI or ARB is recommended for patients with T2DM or for non-African/African-Caribbean patients who are under 55 years of age.<sup>2</sup> See **Table 1** before for full details of step therapy. For those initiating or changing diuretic treatment, thiazide-like agents, such as INDAP, are preferred over conventional thiazide diuretics of HCTZ and bendroflumethiazide.<sup>2</sup> CTDN was removed as an example due to limited availability in the European market and confusion over being listed prior to INDAP in a previous iteration of this guideline.<sup>2</sup> Patients who are well controlled on conventional thiazides should continue those agents.<sup>2</sup>

**Table 1: NICE Guidelines Step Therapy for Hypertension<sup>2</sup>**

Patient Characteristics	Step 1	Step 2	Step 3	Step 4
Type 2 diabetes mellitus <ul style="list-style-type: none"> <li>Regardless of age or family origin</li> </ul>	ACEI or ARB	CCB or thiazide-like diuretic	Combination of: (ACEI or ARB) AND CCB AND thiazide-like diuretic	<p>If potassium 4.5 mEq/L or less consider: Low-dose spironolactone</p> <p>Monitor potassium and use caution in patients with reduced renal function.</p> <p>If potassium 4.5 mEq/L or higher consider: Alpha-blockers or beta-blockers</p>
Age 55 or older <ul style="list-style-type: none"> <li><b>NOT</b> African or African-Caribbean origin</li> </ul>	CCB, if not tolerated use thiazide-like diuretic	ACEI or ARB or thiazide-like diuretic		
Age 55 and older <ul style="list-style-type: none"> <li>African or African-Caribbean Origin</li> </ul>	CCB, if not tolerated use thiazide-like diuretic	ACEI or ARB or thiazide-like diuretic <i>*Consider ARB in preference to ACEI</i>		
Age under 55 years <ul style="list-style-type: none"> <li><b>NOT</b> African or African-Caribbean origin</li> </ul>	ACEI or ARB	ACEI or ARB or thiazide-like diuretic		
Age under 55 years <ul style="list-style-type: none"> <li>African or African-Caribbean Origin</li> </ul>	CCB, if not tolerated use thiazide-like diuretic	ACEI or ARB or thiazide-like diuretic <i>*Consider ARB in preference to ACEI</i>		
Clinical suspicion of heart failure	Consider thiazide-like diuretic, then follow chronic heart failure guidelines			

Department of Veterans Affairs/Department of Defense (VA/DoD)

In 2014, the VA/DoD published an update of the 2004 guidelines on the diagnosis and management of hypertension in the primary care setting.<sup>3</sup> Recommendations for treatment initiation vary by age and comorbidities, but there is a strong recommendation to offer pharmacologic treatment for a SBP of ≥ 160 mmHg in patients 60 years and older, and a weak recommendation to begin pharmacologic treatment with a SBP of ≥ 160 mmHg in patients younger than 60 years old.<sup>3</sup> For patients who are 30 years and older, there is a strong recommendation to offer pharmacologic treatment for DBP of ≥ 90 mmHg, and a weak recommendation to suggest offering pharmacologic treatment for patients 18-29 years with a DBP of ≥ 90 mmHg.<sup>3</sup> The guidelines offer a weak recommendation to initiate combination therapy for patients with a baseline SBP of 20 mmHg or DBP of 10 mmHg above the goal BP based upon an individual patient’s age and comorbidities.<sup>3</sup>

These guidelines have a strong recommendation (grade A) for the use of thiazide-type diuretics as first-line therapy, either as monotherapy or in combination with other agents, with preferred doses of 12.5-25 mg per day for CTDN, 25-50 mg per day for HCTZ, or 2.5 mg per day for immediate-release INDAP.<sup>3</sup> A weak recommendation supports the use of CTDN or INDAP preferentially over HCTZ for treatment initiation or in switching patients who are inadequately controlled on 50 mg per day of HCTZ.<sup>3</sup> Patients with refractory hypertension or who are unable to tolerate triple therapy of ACEI or ARB, CCB, and thiazide-type diuretics

have a number of other pharmacologic classes which can be considered.<sup>3</sup> These include aldosterone receptor antagonists such as spironolactone or eplerenone and other potassium-sparing diuretics, such as amiloride.<sup>3</sup> Preference for one of these classes over another is not specified.<sup>3</sup>

#### American College of Clinical Cardiology (ACC)/American Heart Association (AHA), et al.

The ACC, AHA, and numerous partners published 2017 guidelines for the prevention, detection, evaluation, and management of high BP in adults.<sup>1</sup> Recommendations were delineated by strength based on the anticipated risk and benefit ratio (Class I-III) and quality of evidence (Level A evidence from multiple RCTs or meta-analyses to Level C evidence derived from limited data or expert opinion).<sup>1</sup> Recommended first-line therapy includes thiazide-type diuretics, CCBs, and ACEI/ARBs (Class I, Level A from systematic reviews).<sup>1</sup> Of the thiazide-type diuretics, CTDN has a prolonged half-life and was found to be superior to both amlodipine and lisinopril in preventing HF in head-to-head comparison in the ALLHAT trial.<sup>1</sup> This guideline reported that results from meta-analyses suggest that thiazide-like diuretics, specifically CTDN, are the best choice for first step therapy in patients without contraindications or other important comorbidities (e.g. chronic kidney disease).<sup>1</sup> MRAs, including eplerenone and spironolactone, are preferred agents for primary aldosteronism and as add-on therapy for resistant hypertension. Spironolactone generally has greater incidence of particular adverse events, including gynecomastia and impotence, compared to eplerenone, which usually requires twice daily dosing for BP lowering.<sup>1</sup> Loop diuretics are recommended for symptomatic HF, and potassium sparing agents can be considered for those with hypokalemia on monotherapy with a thiazide-type agent.<sup>1</sup> These nuanced class specific recommendations were not graded.<sup>1</sup>

#### European Society of Cardiology (ESC)/European Society of Hypertension (ESH)

In 2018, ESC/ESH published guidelines for the management of arterial hypertension using identical grading systems for class of recommendation and level of evidence as ACC/AHA type guidelines.<sup>4</sup> Most patients should begin with dual combination treatment as initial therapy with either ACEI or ARB plus a CCB or thiazide-type diuretic (Class I, Level A).<sup>4</sup> INDAP and CTDN have a number of RCTs showing improvement in cardiovascular events.<sup>4</sup> Additionally, they have higher potency than HCTZ without an increased rate in side effects.<sup>4</sup> However, a recent meta-analysis of placebo-controlled RCTs evaluating HCTZ, INDAP, and CTDN found similar rates of CV events.<sup>4</sup> Therefore, in the absence of direct head-to-head comparison between thiazide diuretic HCTZ and thiazide-like diuretics of INDAP and CTDN, the authors do not give preference to one agent over another.<sup>4</sup> Patients with HF and edema should begin loop diuretics over thiazide-type diuretics.<sup>4</sup> Thiazides-type diuretics should be avoided due to lack of efficacy for those with renal impairment.<sup>4</sup> If dual antihypertensive therapy is ineffective, patients should advance to step 2, triple therapy, with an ACEI or ARB PLUS CCB PLUS thiazide-type diuretic. Those patients who remain uncontrolled at step 2, with no additional comorbidities dictating antihypertensive therapy should move to step 3 with the addition of spironolactone, another diuretic (such as a potassium sparing agent), an alpha-blocker, or a beta-blocker.<sup>4</sup> It is noted that a thiazide-type diuretic plus a potassium-sparing diuretic may be equivalent to CCB-based treatment and result in fewer metabolic effects such as hypokalemia and glucose intolerance than the combination of thiazide-type diuretics and BBs.<sup>4</sup> However, the dual diuretic combination was not recommended in preference to a thiazide-type diuretic plus BB combination.<sup>4</sup>

#### Heart Failure

##### National Institute for Health and Care Excellence (NICE)

In 2018, NICE published guidelines for the diagnosis and management of chronic HF in adults.<sup>5</sup> In treating HF<sub>r</sub>EF, an ACEI should be considered first-line therapy in the absence of significant valvular disease and should be titrated upward at short intervals to a maximal tolerated dose. An ARB should be used in patients unable to take an ACEI. Additionally, those without contraindications are recommended to begin a BB indicated for heart failure (e.g. metoprolol succinate or carvedilol), and slowly titrated as tolerated. A MRA can be considered for those already taking an ACEI and BB. Recommendations between different MRA drugs are not made. Other medications, including ivabradine, sacubitril-valsartan, hydralazine plus isosorbide, and digoxin can be considered in specific patients under

specialist consultation. Loop diuretics are recommended for the relief of congestion and fluid retention. Specific preference for one loop agent over another are not included. Non-dihydropyridines and short-acting dihydropyridine medications should be avoided in patients who have HFrEF. A low to medium dose of a loop diuretic should be offered to HFpEF.<sup>5</sup>

#### 2017 ACC/AHA/HFSA Focused Update of the 2013 Guideline for the Management of Heart Failure

The ACC issued a 2017 update of the 2013 guidelines for the management of HF.<sup>6</sup> The recommendation to use diuretics for relief of symptoms related to volume overload from HFpEF (Class I, Level C) remains unchanged from the previous guideline.<sup>6,28</sup> The choice of diuretic for volume overload may include loop, thiazide-type, or potassium-sparing (including spironolactone, but excluding eplerenone).<sup>6,28</sup> A new recommendation is to consider a MRA to decrease hospitalizations for select HFpEF patients meeting all the following criteria (Class IIB, Level B based on RCTs):

- EF  $\geq$  45%,
- Elevated B-type natriuretic peptide (BNP) or HF admission within 1 year,
- Glomerular filtration rate (GFR) over 30 mL/min,
- Serum creatinine less than 2.5 mg/dL, and
- Potassium less than 5 mEq/L.<sup>6</sup>

Recommendations related to diuretic use in HFrEF Stage C and D remain unchanged from the previous full guideline.<sup>28</sup> Step 1 therapy is to initiate an ACEI or ARB plus a BB, with loop diuretic use as needed (Class 1, Level C). Step 2 for HFrEF involves assessment of individual patient parameters. For those with New York Heart Association class II-IV disease and an EF of less than 35%, a MRA is recommended (Class I, Level A).<sup>28</sup> Patients with an EF of 40% or less following an acute myocardial infarction with T2DM or symptoms of HF should also begin MRA therapy (Class I, Level B).<sup>28</sup> Both groups should have a GFR of over 30 mL/min and a serum potassium of less than 5 mEq/L to avoid harm in starting MRA (Class III-harm, Level B).<sup>28</sup>

#### European Society of Cardiology (ESC)/European Society of Hypertension (ESH)

The 2016 ESC/ESH guidelines address the diagnosis and treatment of acute and chronic HF. MRAs are recommended to reduce mortality and risk of HF hospitalization in patients with HFrEF without contraindications (Class I, Level A).<sup>7</sup> Diuretics (loop, thiazide, MRA, or potassium-sparing) can be used to relieve symptoms of congestion (Class I, Level B) and to reduce the risk of HF hospitalization in patients with congestion (Class IIa, Level B).<sup>7</sup> For patients with HFpEF and HFmrEF there has been no reduction in mortality seen with the use of ACEI, ARB, BB, and MRA medications.<sup>7</sup> There is limited evidence that spironolactone may reduce HF hospitalizations in these patients when they are in sinus rhythm.<sup>7</sup> Diuretics continue to be recommended for HFpEF and HFmrEF patients to treat congestion (Class I, Level B).<sup>7</sup>

After review, 5 guidelines were excluded due to poor quality.<sup>55-59</sup> Guidelines for pregnancy were reviewed and excluded as diuretics are generally not recommended for those patients.

#### **New Formulations:**

Spironolactone (Carospir<sup>®</sup>) 25 mg/5mL oral suspension was approved August 2017.

#### **New FDA Safety Alerts:**

No FDA safety alerts involving diuretics from 2014 to 2019.

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**Appendix 1: Current Preferred Drug List**

<b><u>Generic</u></b>	<b><u>Brand</u></b>	<b><u>Form</u></b>	<b><u>PDL</u></b>
hydrochlorothiazide	HYDROCHLOROTHIAZIDE	CAPSULE	Y
hydrochlorothiazide	MICROZIDE	CAPSULE	Y
hydrochlorothiazide	HYDROCHLOROTHIAZIDE	SOLUTION	Y
hydrochlorothiazide	HYDROCHLOROTHIAZIDE	TABLET	Y
indapamide	INDAPAMIDE	TABLET	Y
spironolactone	ALDACTONE	TABLET	Y
spironolactone	SPIRONOLACTONE	TABLET	Y
triamterene	TRIAMTERENE	CAPSULE	Y
amiloride HCl	AMILORIDE HCL	TABLET	Y
spironolact/hydrochlorothiazid	ALDACTAZIDE	TABLET	Y
spironolact/hydrochlorothiazid	SPIRONOLACTONE-HCTZ	TABLET	Y
triamterene/hydrochlorothiazid	DYAZIDE	CAPSULE	Y
triamterene/hydrochlorothiazid	TRIAMTERENE W/HCTZ	CAPSULE	Y
triamterene/hydrochlorothiazid	TRIAMTERENE-HYDROCHLOROTHIAZID	CAPSULE	Y
amiloride/hydrochlorothiazide	AMILORIDE HCL W/HCTZ	TABLET	Y
amiloride/hydrochlorothiazide	AMILORIDE-HYDROCHLOROTHIAZIDE	TABLET	Y
furosemide	FUROSEMIDE	SOLUTION	Y
furosemide	FUROSEMIDE	TABLET	Y
furosemide	LASIX	TABLET	Y
bumetanide	BUMETANIDE	TABLET	Y
torseamide	TORSEMIDE	TABLET	Y
chlorothiazide	DIURIL	ORAL SUSP	N
chlorothiazide	CHLOROTHIAZIDE	TABLET	N
methyclothiazide	METHYCLOTHIAZIDE	TABLET	N
chlorthalidone	CHLORTHALIDONE	TABLET	N
metolazone	METOLAZONE	TABLET	N
spironolactone	CAROSPIR	ORAL SUSP	N
eplerenone	EPLERENONE	TABLET	N
eplerenone	INSPIRA	TABLET	N
triamterene/hydrochlorothiazid	MAXZIDE	TABLET	N
triamterene/hydrochlorothiazid	MAXZIDE-25 MG	TABLET	N
triamterene/hydrochlorothiazid	TRIAMTERENE W/HCTZ	TABLET	N
triamterene/hydrochlorothiazid	TRIAMTERENE-HYDROCHLOROTHIAZID	TABLET	N
ethacrynic acid	EDECIN	TABLET	N
ethacrynic acid	ETHACRYNIC ACID	TABLET	N
furosemide	FUROSEMIDE	SOLUTION	N

## Appendix 2: New Comparative Clinical Trials

A total of 293 citations were manually reviewed from the initial literature search. After further review, 291<sup>30,60-233,234-347</sup> 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 2 trials<sup>25,26</sup> are summarized in the table below. Full abstracts are included in **Appendix 3**.

**Table 1. Description of Randomized Comparative Clinical Trials.**

Study	Comparison	Population	Primary Outcome	Results
Cushman et al <sup>26</sup>  MC, DB, RCT, phase 4	AZL-M/CTDN 20/12.5 mg vs. AZL-M/CTDN 40/12.5 mg vs. OLM/HCTZ 20/12.5 mg <i>All doses to be doubled at week 4 if not at target BP</i>  3 to 4 week washout period of previous antihypertensives before randomization  Stratified by race (i.e. black or nonblack)  8 weeks of treatment	Stage 2 systolic HTN  N=1085	Change SBP from baseline at week 8	AZL-M/CTDN 20/12.5 mg vs. OLM/HCTZ 20/12.5 mg -6.1 mmHg (95% CI -8.4 to -3.8 mmHg; p<0.001) Favors AZL-M/CTDN  AZL-M/CTDN 40/12.5 mg vs. OLM/HCTZ 20/12.5 mg -6.7 mmHg (95% CI -9.1 to -4.4 mmHg; p<0.001) Favors AZL-M/CTDN  Use of different ARB agents in comparison groups makes results difficult to interpret.
Korol et al <sup>25</sup>  MC, DB, RCT, phase 4	Spirolactone 25 mg/day vs. Eplerenone 50 mg/day  16 weeks of treatment	Adults with HF; LVEF ≤ 40%; NYHA class II-IV; T2DM or glucose intolerance; and appropriate background HF pharmacotherapy (BB and ACEI/ARB)  N=62 randomized, 55 analyzed for primary endpoint	Change in HbA <sub>1c</sub> from baseline to 16 weeks  Per protocol analysis	Spirolactone change -0.2% ± 0.83% SD Eplerenone change 0.1% ± 0.38% Between group difference 0.3%; p = 0.2152

Abbreviations: ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; AZL-M = azilsartan medoxomil; BB = beta blocker; BP = blood pressure; CI = 95% confidence interval; CTDN = chlorthalidone; DB = double-blind; HbA<sub>1c</sub> = glycated hemoglobin; HCTZ = hydrochlorothiazide; HF = heart failure; HR = hazard ratio; HTN = hypertension; LVEF = left ventricular ejection fraction; MC = multi-center; NYHA = New York Heart Association; OL = open-label; OLM = olmesartan; RCT = randomized clinical trial; SD=standard deviation; T2DM = type 2 diabetes mellitus.

Author: Fletcher

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### Appendix 3: Abstracts of Comparative Clinical Trials

Cushman WC, Bakris GL, White WB, et al. A randomized titrate-to-target study comparing fixed-dose combinations of azilsartan medoxomil and chlorthalidone with olmesartan and hydrochlorothiazide in stage-2 systolic hypertension. *J Hypertens*. 2018;36(4):947-956

**BACKGROUND:** Azilsartan medoxomil (AZL-M), an angiotensin II receptor blocker, has been developed in fixed-dose combinations (FDCs) with chlorthalidone (CTD).

**OBJECTIVE/METHODS:** We compared FDCs of AZL-M/CTD 20/12.5 mg once daily titrated to 40/25 mg if needed or AZL-M/CTD 40/12.5 mg once daily titrated to 80/25 mg if needed with an olmesartan medoxomil (OLM)-hydrochlorothiazide (HCTZ) 20/12.5 mg FDC once daily titrated to 40/25 mg if needed in a randomized, double-blind, 8-week study of 1085 participants with clinic SBP 160-190 mmHg and DBP 119 mmHg or less. Titration to higher doses occurred at week 4 if BP was at least 140/90 mmHg ( $\geq 130/80$  mmHg if diabetes or chronic kidney disease). The primary endpoint was change from baseline in clinic SBP; 24-h ambulatory BP monitoring was also measured.

**RESULTS:** Greater reductions in clinic SBP from a baseline of 165 mmHg were observed ( $P < 0.001$ ) in both AZL-M/CTD arms (-37.6 and -38.2 mmHg) versus OLM/HCTZ (-31.5 mmHg), despite greater dose titration in the OLM/HCTZ group. At 8 weeks, both AZL-M/CTD FDCs reduced 24-h SBP more than OLM/HCTZ (-26.4 and -27.9 versus -20.7 mmHg; both  $P < 0.001$ ), and higher proportions in both AZL-M/CTD groups achieved target BP compared with the OLM/HCTZ group (69.4 and 68.9 versus 54.7%, both  $P < 0.001$ ). Adverse events leading to drug discontinuation occurred in 6.2, 9.5, and 3.1% with the AZL-M/CTD lower and higher doses, and OLM/HCTZ, respectively.

**CONCLUSION:** This large, titration-to-target BP study demonstrated AZL-M/CTD FDCs to have superior antihypertensive efficacy compared with the maximum approved dose of OLM/HCTZ.

Korol S, White M, O'Meara E, et al. A comparison of the effects of selective and non-selective mineralocorticoid antagonism on glucose homeostasis of heart failure patients with glucose intolerance or type II diabetes: A randomized controlled double-blind trial. *Am Heart J*. 2018;204:190-195.

Mineralocorticoid receptor antagonists (MRAs) decrease morbidity and mortality in patients with heart failure (HF). However, spironolactone, a non-selective MRA, has been shown to exert a harmful effect on glucose homeostasis. The objective of this multicenter, randomized, controlled, double-blind trial was to compare the effects of spironolactone to those of the selective MRA eplerenone on glucose homeostasis among 62 HF patients with glucose intolerance or type II diabetes. Trial registration number: [NCT01586442](https://clinicaltrials.gov/ct2/show/study/NCT01586442)

**Appendix 4: Medline Search Strategy**

Pubmed with MESH terms

#	Searches	Results
1	Limits: Clinical Trial; Clinical Trial, Phase III; Clinical Trial, Phase IV; Comparative Study; Controlled Clinical Trial; Guideline; Meta-Analysis; Multicenter Study; Practice Guideline; Pragmatic Clinical Trial; Randomized Controlled Trial; Systematic Reviews; Publication date from 2014/09/01 to 2019/11/22; Humans; English  Heart Failure/drug therapy OR Hypertension/drug effects OR Hypertension/drug therapy	2740
2	Indapamide/therapeutic use OR Indapamide/toxicity OR Hydrochlorothiazide/therapeutic use OR Hydrochlorothiazide/toxicity OR Spironolactone/therapeutic use OR Spironolactone/toxicity OR Triamterene/therapeutic use OR Triamterene/toxicity OR Amiloride/therapeutic use OR Amiloride/toxicity OR Furosemide/therapeutic use OR Furosemide/toxicity OR Bumetanide/therapeutic use OR Bumetanide/toxicity OR Torsemide/therapeutic use OR Chlorothiazide/therapeutic use OR Chlorothiazide/toxicity OR Methyclothiazide/therapeutic use OR Methyclothiazide/toxicity OR Chlorthalidone/therapeutic use OR Chlorthalidone/toxicity OR Metolazone/therapeutic use OR Eplerenone/therapeutic use) OR Ethacrynic Acid/therapeutic use OR Ethacrynic Acid/toxicity OR Hydroflumethiazide/therapeutic use OR Hydroflumethiazide/toxicity	545
3	#1 AND #2	321

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**Appendix 5: Key Inclusion Criteria**

<b>Population</b>	<b>Adults and pediatrics</b>
<b>Intervention</b>	Diuretic therapy
<b>Comparator</b>	Active control or placebo
<b>Outcomes</b>	Mortality, composite cardiovascular mortality, hospitalizations, blood pressure, safety outcomes (e.g. hyperkalemia, glucose intolerance)
<b>Timing</b>	N/A
<b>Setting</b>	Outpatient

## Orphan Drug Policy: Prior Authorization Update

### Purpose of the Update:

This update identifies 3 candidates for addition to the orphan drug policy due to lack of utilization in FFS since FDA approval (**Table 1**). See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

**Table 1.** Candidates for Addition to the Orphan Drug Policy

Generic Name (Brand)	Diagnosis	Year of Approval	FFS Utilization Since Approval	Relevant ICD-10 codes	FFS patients with claims for relevant ICD-10 codes*
Burosumab-twza (Crysvita®)	X-linked hypophosphatemia (XLH) in children and adults	2018	0	E83.31 Familial hypophosphatemia	5
Cerliponase alfa (Brineura®)	To slow the loss of ambulation in symptomatic pediatric and adolescent patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (also known as tripeptidyl peptidase 1 deficiency or Batten Disease).	2017	0	E75.4 Neuronal ceroid lipofuscinosis	0
Luspatercept (Reblozyl®)	<ul style="list-style-type: none"> <li>Anemia in adults with beta thalassemia who require regular red blood cell transfusion</li> <li>Anemia failing an erythropoiesis stimulating agent and requiring 2 or more RBC units over 8 weeks in adult patients with very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts or with myelodysplastic/ myeloproliferative neoplasm with ring sideroblasts and thrombocytosis</li> </ul>	2019	0	D56.1 Beta thalassemia D56.5 Hemoglobin E-beta thalassemia D46.1 Refractory anemia with ring sideroblasts	D56.1: 18 D56.5: 3 D46.1: 5

\* Estimated based on number of patients with FFS medical claims with the indicated diagnosis over a 1 year period (7/01/2018 to 6/30/2019). Diagnoses are based on ICD-10 codes associated with medical claims data, may not exactly match the FDA-approved indication, and may not reflect members *currently* enrolled in FFS.

### Recommendation:

- Implement PA to support medically appropriate use of burosumab-twza, cerliponase alfa, luspatercept based on FDA labeling.

## Appendix 1. Prescribing Information Highlights

### HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

#### RECENT MAJOR CHANGES

Indications and Usage (1)	9/2019
Dosage and Administration, 25-Hydroxy Vitamin D Supplementation (2.5)	9/2019

#### INDICATIONS AND USAGE

CRYSVITA is a fibroblast growth factor 23 (FGF23) blocking antibody indicated for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric patients 6 months of age and older. (1)

#### DOSAGE AND ADMINISTRATION

For subcutaneous use only (2)

- **Pediatric XLH (6 months and older):**
  - For patients who weigh less than 10 kg, starting dose regimen is 1 mg/kg of body weight rounded to the nearest 1 mg, administered every two weeks (2.2)
  - For patients who weigh more than 10 kg, starting dose regimen is 0.8 mg/kg of body weight rounded to the nearest 10 mg, administered every two weeks. The minimum starting dose is 10 mg up to a maximum dose of 90 mg. (2.2)Dose may be increased up to approximately 2 mg/kg (maximum 90 mg), administered every two weeks to achieve normal serum phosphorus. (2.2)
- **Adult XLH:** Dose regimen is 1 mg/kg body weight rounded to the nearest 10 mg up to a maximum dose of 90 mg administered every four weeks. (2.3)

#### DOSAGE FORMS AND STRENGTHS

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

#### CONTRAINDICATIONS

- With oral phosphate and/or active vitamin D analogs. (4)

- When serum phosphorus is within or above the normal range for age. (4)
- In patients with severe renal impairment or end stage renal disease. (4)

#### WARNINGS AND PRECAUTIONS

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

#### ADVERSE REACTIONS

Most common adverse reactions (≥25% in the CRYSVITA group and > Active Control) in pediatric XLH patients are: pyrexia, injection site reaction, cough, vomiting, pain in extremity, headache, tooth abscess, dental caries. (6.1)

Most common adverse reactions (>5% and in at least 2 patients more than placebo) in adult XLH patients are: back pain, headache, tooth infection, restless leg syndrome, vitamin D decreased, dizziness, constipation, muscle spasms, blood phosphorus increased. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Kyowa Kirin, Inc. at 1-888-756-8657 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 9/2019

## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

**BRINEURA (cerliponase alfa) injection, for intraventricular use**  
**Initial U.S. Approval: 2017**

### RECENT MAJOR CHANGES

Dosage and Administration (2.1)	12/2018, 12/2019
Contraindications (4)	12/2018
Warnings and Precautions (5.1, 5.2)	12/2018

### INDICATIONS AND USAGE

Brineura is a hydrolytic lysosomal N-terminal tripeptidyl peptidase indicated to slow the loss of ambulation in symptomatic pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also known as tripeptidyl peptidase 1 (TPP1) deficiency. (1)

### DOSAGE AND ADMINISTRATION

- Aseptic technique must be strictly observed during preparation and administration. (2.1)
- Brineura should be administered by, or under the direction of, a physician experienced in intraventricular administration. (2.1)
- Prior to each infusion, inspect the scalp for signs of intraventricular access device leakage, failure or potential infection.
- Obtain a sample of CSF for cell count and culture prior to each infusion and if clinically indicated. (2.1)
- Brineura is administered to the cerebrospinal fluid (CSF) by infusion via a surgically implanted reservoir and catheter. (2.1)
- Pre-treatment of patients with antihistamines with or without antipyretics or corticosteroids is recommended 30 to 60 minutes prior to the start of infusion. (2.2)
- The recommended dosage is 300 mg administered once every other week as an intraventricular infusion followed by infusion of Intraventricular Electrolytes over approximately 4.5 hours. (2.2)
- For complete information on preparation, specific intraventricular access device for use, and administration, see the full prescribing information. (2.1, 2.3, 2.4, 2.5)

### DOSAGE FORMS AND STRENGTHS

Injection: Brineura 150 mg/5 mL (30 mg/mL) solution, two single-dose vials per carton co-packaged with Intraventricular Electrolytes Injection 5 mL in a single-dose vial. (3)

### CONTRAINDICATIONS

- Any sign or symptom of acute or unresolved localized infection on or around the device insertion site (e.g. cellulitis or abscess); or suspected or confirmed CNS infection (e.g., cloudy CSF or positive CSF gram stain, or meningitis). (4)
- Any acute intraventricular access device-related complication (e.g., leakage, extravasation of fluid, or device failure). (4)
- Patients with ventriculoperitoneal shunts. (4)

### WARNINGS AND PRECAUTIONS

- **Meningitis and Other Intraventricular Access Device-Related Infections:** Monitor the device insertion site for signs of infection. (4, 5.1)
- **Intraventricular Access Device-Related Complications:** Consult a neurosurgeon for any complications with the implanted device. In case of device-related complication, discontinue the infusion and refer to the device labeling for further instructions. (4, 5.2)
- **Cardiovascular Adverse Reactions:** Monitor vital signs before, during, and post-infusion. Monitor Electrocardiogram (ECG) in patients with a history of bradycardia, conduction disorder, or with structural heart disease, during the infusion. In patients without cardiac abnormalities, perform regular 12-lead ECG evaluations every 6 months. (2.5, 5.3)
- **Hypersensitivity Reactions:** Observe patients during and after the infusion. If a severe hypersensitivity reaction occurs, immediately stop the infusion and initiate appropriate treatment. (5.4)

### ADVERSE REACTIONS

Most common adverse reactions ( $\geq 8\%$ ) are: pyrexia, ECG abnormalities, decreased CSF protein, vomiting, seizures, hypersensitivity, increased CSF protein, hematoma, headache, irritability, pleocytosis, device-related infection, bradycardia, feeling jittery, and hypotension. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact BioMarin at 1-866-906-6100 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2019

## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

**REBLOZYL® (luspaterecept-aamt) for injection, for subcutaneous use**  
**Initial U.S. Approval: 2019**

### RECENT MAJOR CHANGES

Indications and Usage, Myelodysplastic Syndromes (1.2)	04/2020
Dosage and Administration, Beta Thalassemia (2.1)	04/2020
Dosage and Administration, Myelodysplastic Syndromes (2.2)	04/2020
Warnings and Precautions, Hypertension (5.2)	04/2020

### INDICATIONS AND USAGE

REBLOZYL is an erythroid maturation agent indicated for the treatment of:

- Anemia in adult patients with beta thalassemia who require regular red blood cell (RBC) transfusions (1.1).
- Anemia failing an erythropoiesis stimulating agent and requiring 2 or more RBC units over 8 weeks in adult patients with very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) (1.2).
- Limitations of Use: REBLOZYL is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia (1.3).

### DOSAGE AND ADMINISTRATION

- The recommended starting dose is 1 mg/kg once every 3 weeks by subcutaneous injection (2.1, 2.2).
- Review hemoglobin (Hgb) results prior to each administration (2.1, 2.2).
- See full prescribing information for preparation and administration instructions (2.3).

### DOSAGE FORMS AND STRENGTHS

- For injection: 25 mg lyophilized powder in a single-dose vial for reconstitution (3)
- For injection: 75 mg lyophilized powder in a single-dose vial for reconstitution (3)

### CONTRAINDICATIONS

None (4).

### WARNINGS AND PRECAUTIONS

- Thrombosis/Thromboembolism: Increased risk in patients with beta thalassemia. Monitor patients for signs and symptoms of thromboembolic events and institute treatment promptly (5.1).
- Hypertension: Monitor blood pressure (BP) during treatment. Initiate anti-hypertensive treatment if necessary (5.2).
- Embryo-Fetal Toxicity: May cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception (5.3, 8.1, 8.3).

### ADVERSE REACTIONS

The most common (>10%) adverse reactions were fatigue, headache, musculoskeletal pain, arthralgia, dizziness/vertigo, nausea, diarrhea, cough, abdominal pain, dyspnea, and hypersensitivity (6.1).

**To report SUSPECTED ADVERSE REACTIONS, contact Celgene Corporation at 1-888-423-5436 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

### USE IN SPECIFIC POPULATIONS

Lactation: Advise not to breastfeed (8.2).

**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Patient Labeling.**

Revised: 04/2020

Appendix 2. Proposed Prior Authorization Criteria

## Orphan Drugs

**Goal(s):**

To support medically appropriate use of orphan drugs (as designated by the FDA) which are indicated for rare conditions  
 To limit off-label use of orphan drugs

**Length of Authorization:**

Up to 6 months

**Requires PA:**

See Table 1 (pharmacy and physician administered claims)

**Covered Alternatives:**

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

Table 1. Indications for orphan drugs based on FDA labeling

Drug	Indication	Age	Dose	Recommended Monitoring
<u><a href="#">Burosumab-twza (CRYSVITA)</a></u>	<u><a href="#">X-linked hypophosphatemia (XLH)</a></u>	<u><a href="#">≥ 6 months</a></u>	<u><a href="#">Pediatric &lt;18 years: Initial (administered subcutaneously every 2 weeks):</a></u> <ul style="list-style-type: none"> <li>• <u><a href="#">&lt;10 kg: 1mg/kg</a></u></li> <li>• <u><a href="#">≥10 mg: 0.8 mg/kg</a></u></li> </ul> <u><a href="#">Max dose of 2 mg/kg (not to exceed 90 mg)</a></u>  <u><a href="#">Adult: 1 mg/kg monthly (rounded to nearest 10 mg; max 90 mg)</a></u>	<u><a href="#">Baseline and Ongoing Monitoring</a></u> <ul style="list-style-type: none"> <li>• <u><a href="#">Use of active vitamin D analogues or oral phosphate within prior week; concurrent use is contraindicated</a></u></li> <li>• <u><a href="#">Fasting serum phosphorous: do not administer if serum phosphorous is within or above normal range</a></u></li> <li>• <u><a href="#">Renal function: use is contraindicated in ESRD or with severe renal impairment (CrCl &lt;30 mL/min for adults or eGFR &lt;30 mL/min/1.73m<sup>2</sup> for pediatric patients)</a></u></li> <li>• <u><a href="#">25-hydroxy vitamin D levels: supplementation with vitamin D (cholecalciferol or ergocalciferol) is recommended as needed.</a></u></li> </ul>
<u><a href="#">Cerliponase alfa (BRINEURA)</a></u>	<u><a href="#">To slow the loss of ambulation in symptomatic</a></u>	<u><a href="#">3-17 years</a></u>	<u><a href="#">300 mg every other week via intraventricular route</a></u>	<u><a href="#">Baseline Monitoring</a></u> <ul style="list-style-type: none"> <li>• <u><a href="#">Enzymatic or genetic testing to confirm tripeptidyl peptidase 1 deficiency or CLN2 gene mutation</a></u></li> </ul>

	<u>Batten Disease (late infantile neuronal ceroid lipofuscinosis type 2 or TPP1 deficiency)</u>			<ul style="list-style-type: none"> <li><u>Baseline motor symptoms (e.g., ataxia, motor function, etc)</u></li> <li><u>ECG in patients with a history of bradycardia, conduction disorders or structural heart disease</u></li> </ul> <u>Ongoing Monitoring</u> <ul style="list-style-type: none"> <li><u>Disease stabilization or lack of decline in motor symptoms compared to natural history</u></li> </ul>
<u>Luspatercept (REBLOZYL)</u>	<u>Anemia (Hg &lt;11 g/dL) due to beta thalassemia in patients requiring regular red blood cell transfusions</u>  <u>Anemia (Hg &lt;11 g/dL) due to myelodysplastic syndromes with ring sideroblasts or myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis</u>	<u>≥ 18 years</u>	<u>Initial: 1 mg/kg subcutaneously</u>  <u>Max dose of 1.25 mg/kg every 3 weeks for beta thalassemia</u>  <u>Max dose of 1.75 mg/kg every 3 weeks for myelodysplastic syndromes</u>	<u>Baseline Monitoring/Documentation</u> <ul style="list-style-type: none"> <li><u>Number of red blood cell transfusions in the prior 2 months; minimum of 2 RBC units over the prior 8 weeks in patients with myelodysplastic syndromes</u></li> <li><u>Trial and failure of an erythropoiesis stimulating agent in patients with myelodysplastic syndromes</u></li> <li><u>Hemoglobin level</u></li> <li><u>Blood pressure</u></li> </ul> <u>Ongoing Monitoring</u> <ul style="list-style-type: none"> <li><u>Discontinue if there is not a decrease in transfusion burden after 3 maximal doses (about 9-15 weeks)</u></li> <li><u>Hemoglobin level</u></li> <li><u>Blood pressure</u></li> </ul>

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	<b>Yes:</b> Go to #3	<b>No:</b> Pass to RPh. Deny; not funded by the OHP.
3. Is the request for a drug FDA-approved for the indication, age, and dose as defined in <b>Table 1</b> ?	<b>Yes:</b> Go to #4	<b>No:</b> Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
4. Is the request for continuation of therapy in a patient previously approved by FFS?	<b>Yes:</b> Go to <b>Renewal Criteria</b>	<b>No:</b> Go to #5
5. Is baseline monitoring recommended for efficacy or safety (e.g., labs, baseline symptoms, etc) AND has the provider submitted documentation of recommended monitoring parameters?	<b>Yes:</b> Go to #6	<b>No:</b> Pass to RPh. Deny; medical appropriateness.
6. Is this medication therapy being prescribed by, or in consultation with, an appropriate medical specialist?	<b>Yes:</b> Go to #7	<b>No:</b> Pass to RPh. Deny; medical appropriateness.
7. Have other therapies been tried and failed?	<b>Yes:</b> Approve for up to 3 months (or length of treatment) whichever is less  Document therapies which have been previously tried	<b>No:</b> Approve for up to 3 months (or length of treatment) whichever is less  Document provider rationale for use as a first-line therapy

Renewal Criteria		
1. Is there documentation based on chart notes that the patient experienced a significant adverse reaction related to treatment?	<b>Yes:</b> Go to #2	<b>No:</b> Go to #3
2. Has the adverse event been reported to the FDA Adverse Event Reporting System?	<b>Yes:</b> Go to #3  Document provider attestation	<b>No:</b> Pass to RPh. Deny; medical appropriateness
3. Is baseline efficacy monitoring available?	<b>Yes:</b> Go to #4	<b>No:</b> Go to #5

Renewal Criteria		
4. Is there objective documentation of improvement from baseline OR for chronic, progressive conditions, is there documentation of disease stabilization or lack of decline compared to the natural disease progression?	<b>Yes:</b> Approve for up to 6 months Document benefit	<b>No:</b> Pass to RPh. Deny; medical appropriateness
5. Is there documentation of benefit from the therapy as assessed by the prescribing provider (e.g., improvement in symptoms or quality of life, or for progressive conditions, a lack of decline compared to the natural disease progression)?	<b>Yes:</b> Approve for up to 6 months Document benefit and provider attestation	<b>No:</b> Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: [6/2020 \(SS\)](#); 2/2020  
Implementation: [TBD](#)

ProDUR Report for January through March 2020

High Level Summary by DUR Alert

DUR Alert	Example	Disposition	# Alerts	# Overrides	# Cancellations	# Non-Response	% of all DUR Alerts	% Overridden
DA (Drug/Allergy Interaction)	Amoxicillin billed and Penicillin allergy on patient profile	Set alert/Pay claim	8	2	0	6	0.01%	25.0%
DC (Drug/Inferred Disease Interaction)	Quetiapine billed and condition on file for Congenital Long QT Sundrome	Set alert/Pay claim	1,626	413	0	1,210	1.20%	25.4%
DD (Drug/Drug Interaction)	Linezolid being billed and patient is on an SNRI	Set alert/Pay claim	253	54	0	199	0.16%	21.3%
ER (Early Refill)	Previously filled 30 day supply and trying to refill after 20 days (80% = 24 days)	Set alert/Deny claim	89,151	18,333	89	70,718	68.13%	20.6%
ID (Ingredient Duplication)	Oxycodone IR 15mg billed and patient had Oxycodone 40mg ER filled in past month	Set alert/Pay claim	27,956	7,704	14	20,212	21.40%	27.6%
LD (Low Dose)	Divalproex 500mg ER billed for 250mg daily (#15 tabs for 30 day supply)	Set alert/Pay claim	909	171	0	736	0.67%	18.8%
LR (Late Refill/Underutilization)	Previously filled for 30 days supply and refill being billed 40 days later.	Set alert/Pay claim	9	7	0	2	0.01%	77.8%
MC (Drug/Disease Interaction)	Bupropion being billed and patient has a seizure disorder	Set alert/Pay claim	1,006	295	2	707	0.73%	29.3%
MX (Maximum Duration of Therapy)		Set alert/Pay claim	619	205	0	414	0.43%	33.1%
PG (Pregnancy/Drug Interaction)	Accutane billed and client has recent diagnosis history of pregnancy	Set alert/Deny claim	27	20	0	7	0.03%	74.1%
TD (Therapeutic Duplication)	Diazepam being billed and patient recently filled an Alprazolam claim.	Set alert/Pay claim	9,135	2,737	0	6,377	6.93%	30.0%
<b>Totals</b>			<b>130,699</b>	<b>29,941</b>	<b>105</b>	<b>100,588</b>	<b>99.71%</b>	<b>22.9%</b>

**ProDUR Report for January through March 2020**

**Top Drugs in Enforced DUR Alerts**

<b>DUR Alert</b>	<b>Drug Name</b>	<b># Alerts</b>	<b># Overrides</b>	<b># Cancellations &amp; Non-Response</b>	<b># Claims Screened</b>	<b>% Alerts/Total Claims</b>	<b>% Alerts Overridden</b>
ER	Risperdal (Risperidone)	2,129	502	1,627	14,896	14.3%	23.6%
ER	Seroquel (Quetiapine)	4,182	964	3,218	29,478	14.2%	23.1%
ER	Abilify (Aripiprazole)	3,244	580	2,664	24,202	13.4%	17.9%
ER	Lamictal (Lamotrigine)	5,403	1,140	4,263	42,428	12.7%	21.1%
ER	Remeron (Mirtazapine)	1,658	302	1,355	13,532	12.3%	18.2%
ER	Trazodone	6,262	1,228	5,034	56,314	11.1%	19.6%
ER	Zoloft (Sertraline)	6,894	1,344	5,550	63,526	10.9%	19.5%
ER	Lexapro (Escitalopram)	4,167	755	3,412	39,778	10.5%	18.1%
ER	Buspirone (Buspar)	2,878	529	2,349	27,895	10.3%	18.4%
ER	Wellbutrin (Bupropion)	5,683	1,052	4,631	55,312	10.3%	18.5%
ER	Prozac (Fluoxetine)	4,780	799	3,981	47,552	10.1%	16.7%
ER	Celexa (Citalopram)	2,563	400	2,163	27,205	9.4%	15.6%
ER	Diazepam	199	41	158	5,073	3.9%	20.6%
ER	Lorazepam	458	115	343	13,190	3.5%	25.1%
ER	Alprazolam	248	71	177	8,703	2.8%	28.6%
ER	Tramadol	9	2	7	479	1.9%	22.2%
ER	Oxycodone	21	8	13	1,458	1.4%	38.1%
ER	Hydrocodone/APAP	24	10	14	1,838	1.3%	41.7%

**ProDUR Report for January through March 2020**

**Early Refill Reason Codes**

<b>DUR Alert</b>	<b>Month</b>	<b># Overrides</b>	<b>CC-3 Vacation Supply</b>	<b>CC-4 Lost Rx</b>	<b>CC-5 Therapy Change</b>	<b>CC-6 Starter Dose</b>	<b>CC-7 Medically Necessary</b>	<b>CC-13 Emergency Disaster</b>	<b>CC-14 LTC Leave of Absence</b>	<b>CC- Other</b>
ER	January	3,760	131	297	1,064	8	2,090	0	0	170
ER	February	3,380	102	204	910	6	1,946	0	0	212
ER	March	6,378	149	246	915	5	2,748	2,142	2	171
	<b>Total =</b>	<b>13,518</b>	<b>382</b>	<b>747</b>	<b>2,889</b>	<b>19</b>	<b>6,784</b>	<b>2,142</b>	<b>2</b>	<b>553</b>
	<b>Percentage of total overrides =</b>		<b>2.8%</b>	<b>5.5%</b>	<b>21.4%</b>	<b>0.1%</b>	<b>50.2%</b>	<b>15.8%</b>	<b>0.0%</b>	<b>4.1%</b>



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College of Pharmacy

## Retro-DUR Intervention History by Quarter FFY 2019 - 2020

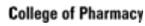
Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Change Form	Fluoxetine Tabs to Caps	Unique Prescribers Identified	953	367		
		Unique Patients Identified	1202	384		
		Total Faxes Successfully Sent	697	280		
		Prescriptions Changed to Recommended Within 6 Months of Intervention	405	103		
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	\$26,367	\$3,229		
	Venlafaxine Tabs to Caps	Unique Prescribers Identified	341	96		
		Unique Patients Identified	371	97		
		Total Faxes Successfully Sent	256	76		
		Prescriptions Changed to Recommended Within 6 Months of Intervention	158	44		
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	\$97,170	\$14,907		



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## Retro-DUR Intervention History by Quarter FFY 2019 - 2020

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Cost Savings	Dose Optimization	Total Claims Identified	64	51		
		Total Faxes Successfully Sent	40	25		
		Prescriptions Changed to Recommended Dose Within 3 Months of Fax Sent	14	7		
		Prescriptions Changed to Alternative Dose Within 3 Months of Fax Sent	12	4		
		Prescriptions Unchanged after 3 Months of Fax Sent	27			
		Safety Monitoring Profiles Identified	4	3		
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Faxes Sent	\$38,315	\$20,418		



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## Retro-DUR Intervention History by Quarter FFY 2019 - 2020

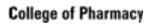
Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Expert Consultation Referral	Antipsychotic Use in Children	Total patients identified	990	675		
		Profiles sent for expert review	10	5		
		Prescribers successfully notified	8	2		
		Patients with continued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



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## Retro-DUR Intervention History by Quarter FFY 2019 - 2020

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Non-Adherence	Antipsychotics for Schizophreniacs	Total patients identified	67	56		
		Total prescribers identified	66	56		
		Prescribers successfully notified	57	51		
		Patients with claims for the same antipsychotic within the next 90 days	33	21		
		Patients with claims for a different antipsychotic within the next 90 days	5	1		



## Retro-DUR Intervention History by Quarter FFY 2019 - 2020

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



## Retro-DUR Intervention History by Quarter FFY 2019 - 2020

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Safety Net	Combination Opioid-Sedative	Total patients identified	93	98		
		Total prescribers identified	93	97		
		Prescribers successfully notified	78	89		
		Patients with discontinuation of therapy within next 90 days	15	39		
		Patients with new prescription for naloxone within next 90 days	2			
		Average number of sedative drugs dispensed within next 90 days	0	0		
		Average number of sedative prescribers writing prescriptions in next 90 days	0	0		
	ICS/LABA	Disqualified	2	4		
		Disqualified - Erroneous denial	2	4		
		Faxes Sent	2	1		
		Fax Sent - Combination Inhaler	1	1		
		Fax Sent - Controller	1			
	TCAs in Children	Total patients identified			5	
		Total prescribers identified			5	
		Prescribers successfully notified			2	

## CGRP Antagonists in Migraine Prophylaxis

Crystal Sharp, Pharm.D. Candidate, Megan Herink, Pharm.D., and Deanna Moretz, Pharm.D OSU Drug Use Research and Management Group

### Introduction

Migraine headache is a common disabling neurological disorder. A headache condition can be classified as chronic migraine (CM) if headaches occur on 15 or more days per month for more than 3 months.<sup>1</sup> Episodic migraine (EM) is a similar condition, but headaches occur less frequently, typically between 4 to 14 days per month.<sup>1</sup> Additionally, headaches must have migraine features (e.g. aura, gastrointestinal symptoms, sensitivity to light) on at least 8 of the 15 migraine days to be considered chronic.<sup>1</sup> Calcitonin Gene-Related Peptide (CGRP) antagonists are the most recent class of preventative migraine therapies. The purpose of this newsletter is to review existing medications used to prevent migraine and the role of CGRP antagonists in patients with migraine.

Several therapies are used for abortive therapy of acute migraine including triptans, ergotamines, non-steroidal anti-inflammatory drugs (NSAIDs), and combination analgesics containing aspirin, caffeine and acetaminophen. These medications are effective for the acute treatment of migraines and are taken at onset of migraine symptoms.

Individuals who experience at least two headaches per month, experience migraines uncontrolled by acute treatment, or have extreme disability from migraines may be eligible for migraine prevention therapies.<sup>2</sup> For patients experiencing greater than 8 migraines per month it is important that a physician assesses for medication overuse, or rebound migraine headaches as this is a common occurrence in patients experiencing an extensive number of headache days per month. Patients can experience medication overuse headaches with the repeated use of analgesics, such as NSAIDs or acetaminophen, if taking  $\geq 15$  days per month for greater than 3 months.<sup>3</sup> Additionally, other analgesics or combinations of medications may lead to rebound headache if used  $\geq 10$  days per month for greater than 3 months.<sup>4</sup>

The goal of preventive therapy is to reduce duration, frequency and severity of migraine attacks, thus improving patient's overall quality of life.<sup>2</sup> Evidence suggests that traditional migraine preventative therapies, such as topiramate, reduce headache frequency as patients were twice as likely to reduce their number of monthly migraine days by 1.2 days when compared with placebo (-1.20; 95% confidence interval (CI) -1.59 to -0.80).<sup>5</sup> The American Academy of Neurology (AAN) and the American Headache Society (AHS) recommendations for the prevention of migraines include agents listed in **Table 1**.

**Table 1. Evidence Level of Existing Migraine Preventative Therapies<sup>6,7</sup>**

Level A - Established Efficacy ( $\geq 2$ Class I studies)			
Topiramate	Metoprolol	Divalproex sodium	
Propranolol	Timolol	Sodium Valproate	
		OnabotulinumtoxinA*	
Level B - Probably Effective (1 Class I or 2 Class II studies)			
Amitriptyline	Venlafaxine	Atenolol	Nadolol

Level C - Possibly Effective (1 Class II study)			
Lisinopril	Candesartan	Clonidine	Guanfacine
Carbamazepine	Nebivolol	Pindolol	Cyproheptadine
Level D - Ineffective or Insufficient Data			
Verapamil	Gabapentin	Bisoprolol	Lamotrigine

\* Recommended for prophylaxis of chronic migraine only.<sup>7</sup>

### Calcitonin Gene-Related Peptide Antagonists

Calcitonin Gene-Related Peptide, a potent pro-inflammatory, pain signaling vasodilator found within the central and peripheral nervous systems, is the main target for new agents aimed at preventing migraines.<sup>8</sup> During migraine attacks, CGRP levels decrease after the administration of triptan agents.<sup>8</sup> Additionally, elevated serum CGRP levels have been found in EM and in even greater levels in CM.<sup>8</sup> New migraine prophylactic agents are targeted monoclonal antibodies with long half-lives, that alter the CGRP pathway by either antagonizing the CGRP receptor complex, or by targeting CGRP itself.<sup>8</sup> The 3 Food and Drug Administration (FDA) approved CGRP antagonists are erenumab (Aimovig<sup>®</sup>), fremanezumab (Ajovy<sup>®</sup>), and galcanezumab (Emgality<sup>®</sup>). All 3 medications are indicated for migraine prophylaxis. Galcanezumab has an additional indication for treatment of cluster headache. Studies that evaluated the CGRP antagonists for prophylaxis of both EMs and CMs are presented in **Table 2**. The definition of CM and EM used in the studies is as previously described in the first paragraph. The primary efficacy outcome in all of the trials was change in monthly (4-week span) migraine days. All studies reported an average reduction between 1.0 to 2.1 migraine days compared to placebo. Trial design for individual drugs are summarized below. A fourth CGRP antagonist, eptinezumab, is currently being studied in Phase 3 trials and additional drugs are in the pipeline. Eptinezumab is administered via intravenous infusion every 3 months, which is a unique route of administration for this class of drugs, as all drugs within this class are administered subcutaneously (SC).

### Erenumab (Aimovig<sup>®</sup>)

Two phase 3 randomized control trials (RCTs), ARISE and STRIVE, evaluated the efficacy of 70 mg and 140 mg monthly erenumab compared to placebo in reducing EM frequency over the span of 3 and 6 months respectively. Both trials included patients with EM who had experienced migraine for at least 12 months prior to study enrollment.<sup>9,10</sup> Those who had failed more than two classes of migraine prevention treatments, had used onabotulinumtoxin-A within 4 months, or used a device for migraine within 2 months of screening were excluded.<sup>9,10</sup> Both trials resulted in a statistically significant reduction in monthly migraine days with erenumab 70 mg (-2.9 to -3.2 days) and 140 mg (-3.7 days) compared to placebo (-1.8 days,  $p < 0.001$  for all comparisons).<sup>9,10</sup> The recommended dose of erenumab is 70 mg injected SC once monthly, with some patients benefiting from 140 mg monthly.<sup>11</sup>

**Fremanezumab (Ajovy®)**

Fremanezumab was evaluated in two phase 3 RCTs for both chronic and episodic migraine prophylaxis.<sup>12,13</sup> Disqualifying criteria included using opioids or barbiturates on more than 4 days during the pretreatment baseline or failing 2 or more preventative migraine medication classes after 3 months of treatment.<sup>12,13</sup> Additionally, use of onabotulinumtoxinA 4 months prior to screening or use of devices for migraine 2 months prior to screening was not permitted.<sup>12,13</sup> Both studies compared fremanezumab 225 mg monthly or 675 mg every three months to placebo. However, in HALO the participants in the monthly arm received a 675 mg injection at baseline followed by a 225 mg injection at weeks 4 and 8. This dosing protocol was not assessed in the EM study.<sup>12,13</sup> In the HALO study, fremanezumab significantly reduced the number of migraine days (675 mg, -4.3 days and 225 mg, -4.6 days) compared to placebo (-2.5 days, p <0.001 for both doses).<sup>13</sup> The recommended dose of fremanezumab is 225 mg SC once a month or 675 mg (given as 3 consecutive injections of 225mg each) every 3 months.<sup>14</sup>

**Galcanezumab (Emgality®)**

Two phase 3 RCTs, EVOLVE-1 and EVOLVE-2, compared galcanezumab 120 or 240 mg monthly to placebo in patients with EM.<sup>15,16</sup> The majority of subjects (60.0% to 65.5%) had previously used migraine preventative agents; however, only 4.9% and 14.3% had failed 2 or more medications respectively.<sup>15,16</sup> Patients were excluded if they failed treatment with three or more migraine prophylactic agents from Level A or Level B in **Table 1**.<sup>15,16</sup> Other exclusion criteria included using opioids or barbiturates more than twice per month or exposure to any therapeutic antibody within the past 12 months.<sup>15,16</sup> These studies differed from previous trials as concomitant use of a migraine prophylactic agent was not permitted.<sup>15,16</sup> The EVOLVE-1 study differed from EVOLVE-2 as it only assessed patients in North America, whereas the latter was a global study.<sup>15</sup> In the EVOLVE-1 study, galcanezumab significantly reduced the number of migraine days (120 mg, -4.7 days and 240 mg, -4.6 days) compared to placebo (-2.8 days p<0.001 with both doses; **Table 2**)<sup>15</sup>. In the EVOLVE-2 study, galcanezumab significantly reduced the number of migraine days (120 mg, -2.02 days and 240 mg, -1.90 days) compared to placebo (-2.3 days p<0.001 with both doses; **Table 2**).<sup>16</sup> The recommended dose of galcanezumab is to begin with a 240mg loading dose followed by monthly doses of 120mg administered via the SC route.<sup>17</sup>

**Safety Data**

In general, CGRP antagonists are well tolerated and discontinuations due to adverse events were similar compared to placebo. The most common adverse events (AEs) reported during clinical trials included injection site pain, induration, and erythema.<sup>9,10,12,13,15,16</sup> Considering CGRP possesses vasodilatory properties that can be released during ischemia, there is a theoretical risk that patients with existing cardiovascular conditions may be at a higher risk for a cardiac event when CGRP is inhibited.<sup>9</sup> In the ARISE trial, it was noted that cardiac related AEs were low and did not differ between comparators.<sup>9</sup> However, ARISE excluded patients with history of myocardial infarction, stroke, transient ischemic attack, unstable angina, coronary artery bypass surgery, or revascularization 12 months prior to study screening.<sup>9</sup> Therefore, more data is needed to delineate cardiovascular risk.

**Table 2. Study Results for CGRP Antagonists<sup>7-11</sup>**

Diagnosis		Study Comparator Arms	Primary Endpoint: Change in Monthly Migraine Days
<b>Erenumab</b>			
<b>ARISE</b> (N=577) <sup>9</sup>	Episodic Migraine	70 mg monthly vs. Placebo	LSMD -1.0 95% CI -1.6 to -0.5 p<0.001
<b>STRIVE</b> (N=955) <sup>10</sup>	Episodic Migraine	70 mg monthly or 140 mg monthly vs. Placebo	<b>70 mg vs. placebo</b> LSMD -1.4 95% CI -1.9 to -0.9 p<0.001 <b>140 mg vs. placebo</b> LSMD -1.9 95% CI -2.3 to -1.4 p<0.001
<b>Fremanezumab</b>			
<b>HALO</b> <sup>13</sup> (N=1130)	Chronic Migraine	675 mg every 3 months or 675 mg LD, 225 mg monthly vs. Placebo	<b>675 mg vs. placebo</b> LSMD -1.8 p<0.001 CI NR <b>225 mg vs. placebo</b> LSMD -2.1 p<0.001 CI NR
<b>Dodick DW, et al.</b> <sup>12</sup> (N=875)	Episodic Migraine	675 mg every 3 month or 225 mg monthly vs. Placebo	<b>675 mg vs. placebo</b> LSMD -1.3 95% CI -1.79 to -0.72 p<0.001 <b>225 mg vs. placebo</b> LSMD -1.5 95% CI -2.01 to -0.93 p<0.001
<b>Galcanezumab</b>			
<b>EVOLVE-1</b> <sup>15</sup> (N=858)	Episodic Migraine	120 mg monthly or 240 mg monthly vs. Placebo	<b>120 mg vs. placebo</b> LSMD -1.9 95% CI -2.5 to -1.4 p<0.001 <b>240 mg vs. placebo</b> LSMD -1.8 95% CI -2.3 to -1.2 p<0.001
<b>EVOLVE-2</b> <sup>16</sup> (N=915)	Episodic Migraine	120 mg monthly or 240 mg monthly vs. Placebo	<b>120 mg vs. placebo</b> LSMD -2.0 95% CI -2.6 to -1.5 p<0.001 <b>240 mg vs. placebo</b> LSMD -1.9 95% CI -2.4 to -1.4 p<0.001
Abbreviations: CI=confidence interval; LD=loading dose; LSMD=least squares mean difference; mg=milligrams; N=number; NR=not reported			

**Study Limitations**

Several limitations were identified in an analysis of the CGRP antagonist studies. All studies excluded participants who had previously failed a certain number of migraine prophylactic agents. Also, the number of prophylaxis naïve patients was surprisingly high, thus making it difficult to apply efficacy and safety data from these studies to individuals in which CGRP antagonists are most likely indicated. Additionally, several studies enrolled a majority of Caucasian female subjects, therefore evidence is greatly limited in males and other ethnic groups. All of the studies analyzed compared their treatment to placebo only, despite the fact that there are a number of well-established prophylactic agents that are used in practice. Lastly, trials analyzed patient responses over a short period of three to six months and the absolute change in monthly migraine days was modest at best. Due to evidence limitations and high cost of CGRP inhibitor therapies (**Figure 1**), traditional migraine preventative agents are still recommended by the AAN/AHA and are outlined in **Table 1**.

**Figure 1. Monthly Migraine Prevention Agents\***



\* Costs based on a 30-day supply of approved max daily dosages for migraine prevention. Costs obtained from the Oregon Health Authority's Average Actual Acquisition Cost (AAAC) Rate Listing Effective as of September 17, 2019.

\*\* 30-day cost estimate is based on average wholesale price (AWP).

**Conclusion**

The CGRP antagonist class has demonstrated efficacy in reducing the average monthly migraine days compared to placebo. Short-term studies, exclusion of patients with comorbidities and lack of direct comparative efficacy and safety evidence between the CGRP antagonists are limitations to current evidence. For these reasons, all CGRP antagonists require prior authorization prior to dispensing in the Medicaid Fee-For-Service population.

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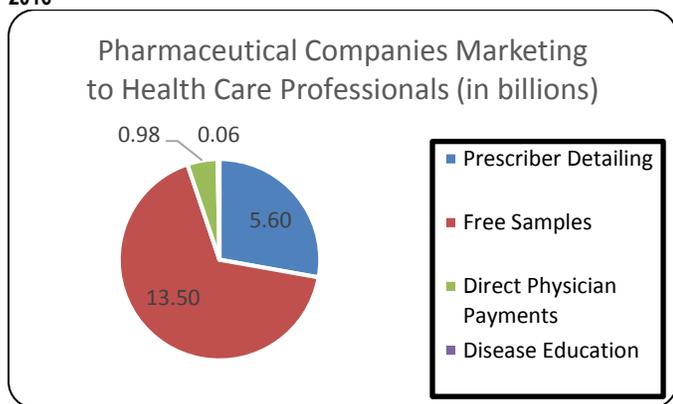
## Evidence for Drugs that are Heavily Marketed

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Direct-to-consumer (DTC) advertising of pharmaceuticals is only allowed in 2 countries worldwide, the United States (U.S.) and New Zealand. Billions of US dollars are spent on DTC advertising on an annual basis. The utility of such marketing has not been associated with improved patient outcomes, but does correlate with increased public interest in promoted drugs.<sup>1</sup> Constructive conversations between providers and their patients are a critical part of making informed evidence-based drug therapy choices. The purpose of this newsletter is to evaluate the evidence for commonly marketed drugs, determine place in therapy, and suggest more cost effective treatment options.

A recent study published in the *Journal of the American Medical Association* (JAMA) found that DTC advertising increased from \$2.1 billion dollars in 1997 to \$9.6 billion dollars in 2016.<sup>2</sup> The primary drivers of the increased advertisement spending were high-cost biologicals and cancer immunotherapies. Marketing to health care professionals also increased from \$15.6 billion to \$20.3 billion within the same 19-year time span (Figure 1).<sup>2</sup> Since 1997, \$11 billion in fines for off-label or deceptive marketing have also been paid out by drug companies.<sup>2</sup> Manufacturers are willing to invest in DTC advertising because of the proven influence on prescribing practices.<sup>1</sup>

**Figure 1. Dollars Spent on Marketing to Health Care Professionals in 2016<sup>2</sup>**



The most actively marketed drugs change from year to year. In 2019, Xeljanz<sup>®</sup>/Xeljanz XR<sup>®</sup>, Ocrevus<sup>®</sup>, Latuda, and Ozempic<sup>®</sup> television commercials were among the most commonly advertised.

### Xeljanz<sup>®</sup>/Xeljanz XR<sup>®</sup> (tofacitinib)

Over \$150 million have been spent annually on TV marketing for tofacitinib, a Janus kinase (JAK) inhibitor approved for the treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA), and moderate-to-severe ulcerative colitis (UC).<sup>3</sup> Advertising for tofacitinib promotes decreased swelling, pain, and joint damage in patients with RA.<sup>4</sup> However, studies of tofacitinib were not able to conclusively show a benefit in progression of structural damage.<sup>5</sup> At 3 months, 31% of patients treated with tofacitinib therapy had symptom reduction compared to 12% of patients on placebo, based on the American College of Rheumatology ACR50 endpoint. ACR50 criteria require at least a 50% reduction in tender and swollen joints and 50% improvement in at least 3 other patient or physician assessments. The ACR50 was 29% for patients with RA who were on methotrexate and tofacitinib versus 8% for patients on methotrexate and placebo.<sup>6</sup> Conventional disease-modifying anti-rheumatic drugs like methotrexate, leflunomide, or sulfasalazine are recommended prior to biologic therapy for RA.<sup>7</sup>

The use of tofacitinib in moderate-to-severe UC is indicated after treatment failure with corticosteroids or tumor necrosis factor (TNF) blockers.<sup>8</sup> No trials have compared tofacitinib to another active treatment in patients with UC to elucidate place in therapy. The absolute difference between tofacitinib and placebo in the number of patients with UC who obtained remission at 52 weeks has ranged from 23-30%.<sup>6</sup> Conventional immunosuppressants (e.g., mercaptopurine, azathioprine, or budesonide) are recommended first for treatment of UC before treatment with a biologic agent.<sup>8</sup>

Tofacitinib carries a Food and Drug Administration (FDA) boxed warning for risk of serious infection, mortality, malignancy and thrombosis, so it especially important to carefully consider the risks versus benefits of therapy.<sup>6</sup>

- Oregon Health Plan (OHP) Fee-For-Service (FFS) policy requires a prior authorization approval for all biologics used for autoimmune diseases
- A trial of conventional treatments are required before approval of biologic therapy
- The cost of first-line treatments, such as methotrexate, are \$7 compared to \$4300 for tofacitinib, based on the 30-day average actual acquisition cost (AAAC)\*

\* Myers and Stauffer. Oregon Health Authority Average Actual Acquisition Cost (AAAC) Rate Listing for Generic Drugs. December 21, 2019.

### Ocrevus<sup>®</sup> (ocrelizumab)

Ocrelizumab is approved for treatment of multiple types of multiple sclerosis (MS) in adults, including clinically isolated syndrome, relapsing-remitting disease (RRMS), active secondary progressive disease, and primary progressive multiple sclerosis (PPMS).<sup>9</sup> In November 2019, the total spending on TV advertisements for ocrelizumab was \$17.6 million.<sup>3</sup> The advertisements promoted reduction in relapses for patients with RRMS, as well as slowing disability of progression in PPMS and relapsing MS (RMS).<sup>10</sup> Most patients with RRMS in these studies only had mild disability. An evidence summary from these ocrelizumab trials are as follows:

- Evidence for ocrelizumab in patients with PPMS is of low quality. Disease progression over 12 weeks (as assessed by the Expanded Disability Score [EDSS]) occurred in 32.9% of patients treated with ocrelizumab and 39.3% of patients on placebo (absolute risk reduction [ARR] 6.4% and number-needed-to-treat [NNT] 16).<sup>11</sup>
- More patients with PPMS treated with ocrelizumab dropped out of trials early versus patients on placebo, potentially falsely increasing the percentage of patients with disability progression, which could have biased the results in favor of ocrelizumab.
- The efficacy of ocrelizumab appears to wane after 18 weeks in patients with PPMS.<sup>11</sup>
- When ocrelizumab was compared to interferon beta-1a in patients with RRMS over 96 weeks, the annualized relapse rates (average number of relapses a group of patients in the study had in one year) were 0.16 and 0.29, respectively, in studies that provided moderate quality evidence.<sup>11</sup>

Ocrelizumab is associated with a higher rate of infusion-related reactions compared to beta-1a in patients with RRMS (34% vs. 10%).<sup>9</sup>

- Interferons are recommended first-line for the management of MS and are the most cost-effective option
- Ocrelizumab is available for OHA FFS patients if clinical prior authorization criteria are met

### Latuda (lurasidone)

Lurasidone is indicated for treatment of schizophrenia and bipolar depression (bipolar I disorder) in adults and pediatric patients, as monotherapy or as adjunctive therapy with lithium or valproate.<sup>12</sup> TV advertisements for lurasidone use in bipolar depression exceeded \$26 million in a 2-month period of October and November 2019.<sup>3</sup> Commercials offered vague statements about the drug's efficacy, such as "efficacy is proven for many people with bipolar depression" and that "it is the number one prescribed therapy for bipolar depression."<sup>13</sup> Patients with bipolar depression treated with lurasidone reported 4.7-point improvement in the Montgomery-Asberg Depression Rating Scale [MADRS] versus patients on placebo (-15.4 points vs. -10.7 points, respectively).<sup>12</sup> When lurasidone was studied as adjunctive therapy with lithium or valproate, patients on lurasidone improved by 3.6 points more on the MADRS than patients on placebo with lithium or valproate.<sup>12</sup> The observed improvements in MADRS scores were significant but none of the studies demonstrated remission of depression, as indicated by a MADRS score of less than or equal to 12.<sup>14</sup> No evidence of efficacy was found for doses greater than 60 mg per day. Lurasidone has a FDA boxed warning for the risk of increased mortality in elderly patients and increased risk of suicidal thoughts.<sup>12</sup>

- For acute bipolar depression, first-line therapies recommended by the Mental Health Clinical Advisory Group (MHCAG) include lamotrigine, lithium, and quetiapine
- Lurasidone is only recommended as 2<sup>nd</sup>-line therapy for acute bipolar depression
- MHCAG treatment algorithms for schizophrenia and bipolar disorder are available at: <https://www.oregon.gov/oha/HSD/OHP/Pages/PT-MHCAG.aspx>
- The cost of lurasidone is more than 20-times higher than olanzapine, which is also approved for bipolar I disorder

### Ozempic® (semaglutide)

Semaglutide is a once-weekly glucagon-like peptide receptor agonist (GLP-1 RA) indicated for adults with type 2 diabetes mellitus (T2DM) as an adjunct to diet and exercise.<sup>15</sup> TV advertisement expenditures for semaglutide are about \$15 million per month.<sup>3</sup> Commercials emphasize glucose lowering and cardiovascular (CV) risk. Hemoglobin A1c (HbA1c) reductions observed with semaglutide are similar to other GLP-1 RAs, ranging from -0.27% to -1.56%.<sup>16</sup> However, patient outcomes beyond 2 years is unknown. The FDA requires all diabetes therapies undergo CV risk assessment. Some T2DM treatments have shown to reduce CV risk in patients, but no increase or decrease in CV risk has been demonstrated with semaglutide.<sup>15</sup> Adverse events associated with semaglutide, most commonly gastrointestinal effects, are similar to other GLP-1 RAs.<sup>15</sup>

- OHA FFS policy recommends semaglutide after trial or contraindication to metformin and sulfonylurea
- Semaglutide is not on the OHP FFS preferred drug list
- Semaglutide is about 30% more expensive than the weekly formulation of exenatide, which is a preferred drug on the OHP FFS preferred drug list\*

\* Myers and Stauffer. Oregon Health Authority Average Actual Acquisition Cost (AAAC) Rate Listing for Generic Drugs. 21 December 2019.

### Conclusion

The DTC advertising concept has captured market share and influenced prescribers and patients for years. Newer, heavily marketed therapies have been shown to be effective in short-term studies, but often lack evidence to show improved patient outcomes over similar, yet more established therapies. With health care costs in the U.S. unlike any developed nation, it is important that evidenced-based therapies that have demonstrated efficacy and safety over time are used first before new drugs with insufficient evidence of clinical superiority are prescribed.

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## Prior Authorization Criteria Update: Multiple Sclerosis

### Purpose of Update:

The Oregon Pharmacy & Therapeutic Committee (P&T) last reviewed evidence for multiple sclerosis agents in November 2017. This update describes proposed prior authorization (PA) changes to accommodate expanded FDA-approved indications for multiple sclerosis products until an evidence review can be completed. Many multiple sclerosis products, which were previously approved for relapsing-remitting disease, received expanded indications in late 2019 for all forms of relapsing multiple sclerosis including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease. A report from the Drug Effectiveness Review Project (DERP) on new evidence of multiple sclerosis drugs is scheduled for review later this year. In addition, PA changes are recommended to remove daclizumab from the prior authorization criteria as it has been voluntarily recalled from the U.S. market due to safety concerns.<sup>1</sup>

### Recommendation:

- Update prior authorization criteria to accommodate expanded FDA-indications.

### References:

1. US Food and Drug Administration. FDA working with manufacturers to withdraw Zinbryta from the market in the United States. Updated March 14, 2018. Accessed May 5 2020. <https://www.fda.gov/drugs/drug-safety-and-availability/fda-working-manufacturers-withdraw-zinbryta-market-united-states>.

### Appendix 1. Prior Authorization Criteria

## Oral Multiple Sclerosis Drugs

### Goal(s):

- Promote safe and effective use of oral disease-modifying multiple sclerosis drugs
- Promote use of preferred multiple sclerosis drugs.

### Length of Authorization:

- Up to 6 months

**Requires PA:**

- Fingolimod
- Teriflunomide
- Dimethyl Fumarate or Diroximel Fumarate

**Covered Alternatives:**

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. <del>Does the patient have a diagnosis of relapsing-remitting Multiple Sclerosis? Is the request for an FDA-approved form of multiple sclerosis?</del>	<b>Yes:</b> Go to #3	<b>No:</b> Pass to RPh. Deny; medical appropriateness.
3. Will the prescriber consider a change to a preferred product?  <u>Message:</u> <ul style="list-style-type: none"><li>• Preferred products are reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics Committee and do not require PA.</li></ul>	<b>Yes:</b> Inform prescriber of covered alternatives in class.	<b>No:</b> Go to #4
4. Is the medication being prescribed by or in consultation with a neurologist?	<b>Yes:</b> Go to #5	<b>No:</b> Pass to RPh. Deny; medical appropriateness.
5. Is the patient on concurrent treatment with a disease modifying drug (i.e. interferon beta 1B, glatiramer acetate, interferon beta 1A, natalizumab, mitoxantrone)?	<b>Yes:</b> Pass to RPh. Deny; medical appropriateness.	<b>No:</b> Go to #6
6. Is the prescription for teriflunomide?	<b>Yes:</b> Go to #7	<b>No:</b> Go to #9
7. Is the patient of childbearing potential?	<b>Yes:</b> Go to #8	<b>No:</b> Approve for up to 6 months.

Approval Criteria		
8. Is the patient currently on a documented use of reliable contraception and is there documentation of a negative pregnancy test prior to initiation of teriflunomide?	<b>Yes:</b> Approve for up to 6 months.	<b>No:</b> Pass to RPh. Deny; medical appropriateness.
9. Is the prescription <u>for</u> fingolimod?	<b>Yes:</b> Go to #10	<b>No:</b> Go to #13
10. Does the patient have evidence of macular edema?	<b>Yes:</b> Pass to RPh. Deny; medical appropriateness.	<b>No:</b> Go to #11
11. Does the patient have preexisting cardiac disease, risk factors for bradycardia, or is on anti-arrhythmic, beta-blockers, or calcium channel blockers?	<b>Yes:</b> Go to #12	<b>No:</b> Approve up to 6 months.
12. Has the patient had a cardiology consultation before initiation (see clinical notes)?	<b>Yes:</b> Approve up to 6 months.	<b>No:</b> Pass to RPh. Deny; medical appropriateness.
13. Is the prescription for dimethyl <u>or diroximel</u> fumarate?	<b>Yes:</b> Go to # 14	<b>No:</b> Pass to RPh. Deny; medical appropriateness.
14. Does patient have a baseline CBC with lymphocyte count greater than 500/ $\mu$ L?	<b>Yes:</b> Approve for up to 6 months.	<b>No:</b> Pass to RPh. Deny; medical appropriateness.

#### Fingolimod Clinical Notes:

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

#### Teriflunomide Clinical Notes:

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

#### Dimethyl Fumarate Clinical Notes:

- Dimethyl fumarate may decrease a patient's white blood cell count. In the clinical trials the mean lymphocyte counts decreased by approximately 30% during the first year of treatment with dimethyl fumarate and then remained stable. The incidence of infections (60% vs. 58%) and serious infections (2% vs. 2%) was similar in patients treated with dimethyl fumarate or placebo, respectively. There was no increased incidence of serious infections observed in patients with lymphocyte counts  $<0.8 \times 10^3$  cells/mm<sup>3</sup> (equivalent to  $<0.8$  cells/ $\mu$ L). A transient increase in mean eosinophil counts was seen during the first 2 months of therapy.
- Dimethyl fumarate should be held if the WBC falls below  $2 \times 10^3$  cells/mm<sup>3</sup> or the lymphocyte count is below  $0.5 \times 10^3$  cells/mm<sup>3</sup> (cells/ $\mu$ L) and permanently discontinued if the WBC did not increase to over  $2 \times 10^3$  cells/mm<sup>3</sup> or lymphocyte count increased to over  $0.5 \times 10^3$  cells/mm<sup>3</sup> after 4 weeks of withholding therapy.
- Patients should have a CBC with differential monitored on a quarterly basis

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

## ~~Daclizumab (Zinbryta™) and Ocrelizumab (Ocrevus™)~~

#### Goal(s):

- Restrict use of ~~daclizumab and~~ ocrelizumab to patients with relapsing-remitting multiple sclerosis (RRMS) or primary progressive multiple sclerosis (PPMS) who have failed multiple drugs for the treatment of PPMS or RRMS.
- Ensure appropriate baseline monitoring to minimize patient harm.

#### Length of Authorization:

- 6 to 12 months

#### Requires PA:

~~Zinbryta™ (daclizumab)~~

- Ocrevus™ (ocrelizumab) pharmacy or physician administered claims

**Covered Alternatives:**

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the medication FDA-approved or compendia-supported for the requested indication?	<b>Yes:</b> Go to #3	<b>No:</b> Pass to RPh. Deny; medical appropriateness
3. Is the drug being used to treat an OHP-funded condition <del>AND is the requested treatment funded by the OHP for that condition?</del>  <del>Note: Treatments referenced on an unfunded line of the prioritized list are not funded by the OHP.</del>	<b>Yes:</b> Go to #4	<b>No:</b> Pass to RPh. Deny; not funded by the OHP.
4. Is this a request for continuation of therapy?	<b>Yes:</b> Go to <b>Renewal Criteria</b>	<b>No:</b> Go to #5
5. Is the patient an adult (age ≥18 years) diagnosed with relapsing <del>remitting</del> multiple sclerosis <del>(RRMS)</del> ?	<b>Yes:</b> Go to #6	<b>No:</b> Go to # <del>10</del> <u>7</u>
6. Has the patient failed trials for at least 2 drugs indicated for the treatment of <del>RRMS</del> <u>relapsing multiple sclerosis</u> ?	<b>Yes:</b> Document drug and dates trialed: 1. _____ (dates) 2. _____ (dates)  Go to #7	<b>No:</b> Pass to RPh. Deny; medical appropriateness
<del>Is the drug daclizumab?</del>	<del><b>Yes:</b> Go to # 8</del>	<del><b>No:</b> Go to # 10</del>
<del>Does the patient have a higher degree of ambulatory ability (e.g., Expanded Disability Status Scale score ≤5)</del>	<del><b>Yes:</b> Go to #9</del>	<del><b>No:</b> Pass to RPh. Deny; medical appropriateness</del>

Approval Criteria		
Does the patient have hepatic disease or hepatic impairment, including ALT or AST $\geq 2$ -times the upper limit of normal, or have a history of auto-immune hepatitis?	<b>Yes:</b> Pass to RPh. Deny; medical appropriateness	<b>No:</b> Go to #12
Is the drug ocrelizumab?	<b>Yes:</b> Go to # 11	<b>No:</b> Pass to RPh. Deny; medical appropriateness
7. Has the patient been screened for an active Hepatitis B infection?	<b>Yes:</b> Go to #12	<b>No:</b> Pass to RPh. Deny; medical appropriateness
8. Is the <u>drug</u> prescribed <u>by or in consultation with</u> a neurologist who regularly treats <u>RMS</u> <u>multiple sclerosis</u> ?	<b>Yes:</b> Approve <del>daclizumab 150 mg once monthly for 6 months</del> or ocrelizumab 300 mg every 2 weeks x 2 doses followed by 600mg IV every 6 months for 12 months	<b>No:</b> Pass to RPh. Deny; medical appropriateness

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

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

## Dalfampridine

### Goal(s):

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

### Length of Authorization:

- Up to 12 months

**Requires PA:**

Dalfampridine

**Covered Alternatives:**

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have a diagnosis of Multiple Sclerosis?	<b>Yes:</b> Go to #3	<b>No:</b> Pass to RPh. Deny; medical appropriateness
3. Is the medication being prescribed by or in consultation with a neurologist?	<b>Yes:</b> Go to #4	<b>No:</b> Pass to RPh. Deny; medical appropriateness
4. Is the request for continuation of therapy previously approved by the FFS program (patient has completed 2-month trial)?	<b>Yes:</b> Go to <b>Renewal Criteria</b>	<b>No:</b> Go to #5
5. Does the patient have a history of seizures?	<b>Yes:</b> Pass to RPh. Deny; medical appropriateness	<b>No:</b> Go to #6
6. Does the patient have moderate or severe renal impairment (est. GFR <50 mL/min)?	<b>Yes:</b> Pass to RPh. Deny; medical appropriateness	<b>No:</b> Go to #7
7. Is the patient ambulatory with a walking disability requiring use of a walking aid <b>OR</b> ; have moderate ambulatory dysfunction and does not require a walking aid <b>AND</b> able to complete the baseline timed 25-foot walk test between 8 and 45 seconds?	<b>Yes:</b> Approve initial fill for 2-month trial.	<b>No:</b> Pass to RPh. Deny; medical appropriateness

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

**Clinical Notes:**

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

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

## Peginterferon Beta-1a (Plegridy®)

**Goal(s):**

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

**Length of Authorization:**

- Up to 12 months

**Requires PA:**

Non-preferred drugs

**Covered Alternatives:**

- Preferred alternatives listed at [www.orpdl.org](http://www.orpdl.org)

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. <u>Is the request for an FDA-approved form of multiple sclerosis?</u> <del>Does the patient have a diagnosis of relapsing-remitting Multiple Sclerosis?</del>	<b>Yes:</b> Go to #3.	<b>No:</b> Pass to RPH; Deny for medical appropriateness.
3. Will the prescriber consider a change to a Preferred MS product?	<b>Yes:</b> Inform provider of covered alternatives in the class. Additional information can be found at <a href="http://www.orpdl.org">www.orpdl.org</a> .	<b>No:</b> Go to #4.
4. Is the medication being prescribed by or in consultation with a neurologist?	<b>Yes:</b> Go to #5.	<b>No:</b> Pass to RPH; Deny for medical appropriateness.
5. Does the patient have any of the following: <ul style="list-style-type: none"> <li>• Adherence issues necessitating less frequent administration</li> <li>• Dexterity issues limiting ability to administer subcutaneous injections</li> </ul>	<b>Yes:</b> Approve for up to one year.	<b>No:</b> Pass to RPH; Deny for medical appropriateness.

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

## Prior Authorization Proposal: Oncology Agents

### Purpose for the Proposal:

The purpose of the prior authorization (PA) proposal is to ensure medically appropriate use of antineoplastic agents, both those recently approved and those approved by the United States Food and Drug Administration (FDA) in the future.

### Background:

Oncology is a rapidly growing area of drug development. In 2017, the FDA approved 12 novel drug therapies as well as 2 gene therapies for oncology.<sup>1-3</sup> In 2018 and 2019, there were 27 novel agents FDA-approved for oncology indications. Additional indications beyond the first FDA approval are often studied in clinical trials for these agents as well and many obtain subsequent new or expanded indication approvals. According to Oregon Administrative Rule 410-120-1200(2)(i), the Division of Medical Assistance Programs will not cover services or items considered experimental or investigational, including clinical trials and demonstration projects, or services that deviate from acceptable and customary standards of medical practice or for which there is insufficient outcome data to indicate efficacy.<sup>4</sup> Off-label use beyond FDA-approved indications may be considered when supported by Centers for Medicare and Medicaid Services (CMS) compendia. One of the most commonly used guidelines for oncology is the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines<sup>®</sup>), which are supported by CMS as a compendia for “use in the determination of a ‘medically-accepted indication’ of drugs and biologicals used off-label in an anticancer chemotherapeutic regimen”.<sup>5,6</sup> NCCN guidelines strongly encourage enrollment in clinical trials for any patient with cancer in order to get the best therapy management. While the Oregon Health Authority is statutorily unable to cover experimental or investigational treatments, access to clinical trials is supported, and appropriate standard of care for patients enrolled in a clinical trial would be covered.

In addition, the Health Evidence Review Commission provides the following guidance for patient-centered care of advanced cancer.<sup>7</sup>

#### GUIDELINE NOTE 12, PATIENT-CENTERED CARE OF ADVANCED CANCER

Cancer is a complex group of diseases with treatments that vary depending on the specific subtype of cancer and the patient’s unique medical and social situation. Goals of appropriate cancer therapy can vary from intent to cure, disease burden reduction, disease stabilization and control of symptoms. Cancer care must always take place in the context of the patient’s support systems, overall health, and core values. Patients should have access to appropriate peer-reviewed clinical trials of cancer therapies. A comprehensive multidisciplinary approach to treatment should be offered including palliative care services (see STATEMENT OF INTENT 1, PALLIATIVE CARE).

Treatment with intent to prolong survival is not a covered service for patients who have progressive metastatic cancer with:

- A) Severe co-morbidities unrelated to the cancer that result in significant impairment in two or more major organ systems which would affect efficacy and/or toxicity of therapy; OR
- B) A continued decline in spite of best available therapy with a non-reversible Karnofsky Performance Status or Palliative Performance score of <50% with ECOG performance status of 3 or higher which are not due to a pre-existing disability.

Treatments with intent to relieve symptoms or improve quality of life are covered as defined in STATEMENT OF INTENT 1, PALLIATIVE CARE.

Examples include:

- A) Single-dose radiation therapy for painful bone metastases with the intent to relieve pain and improve quality of life.
- B) Surgical decompression for malignant bowel obstruction. Single fraction radiotherapy should be given strong consideration for use over multiple fraction radiotherapy when clinically appropriate (e.g., not contraindicated by risk of imminent pathologic fracture, worsening neurologic compromise or radioresistant histologies such as sarcoma, melanoma, and renal cell carcinoma)
- C) Medication therapy such as chemotherapy with low toxicity/low side effect agents with the goal to decrease pain from bulky disease or other identified complications. Cost of chemotherapy and alternative medication(s) should also be considered.

To qualify for treatment coverage, the cancer patient must have a documented discussion about treatment goals, treatment prognosis and the side effects, and knowledge of the realistic expectations of treatment efficacy. This discussion may take place with the patient's oncologist, primary care provider, or other health care provider, but preferably in a collaborative interdisciplinary care coordination discussion. Treatment must be provided via evidence-driven pathways (such as NCCN, ASCO, ASH, ASBMT, or NIH Guidelines) when available.

Both oral and parenteral oncology drugs are typically studied in multiple indications, may have safety concerns, and are generally of high cost. Therefore, a broad PA policy that requires use to align with FDA-approved or NCCN-supported indications and HERC guideline note 12 would ensure appropriate use of these agents. Current policies implemented by other state Medicaid agencies and 2 Coordinated Care Organizations were considered during policy development. Feedback was also solicited from 2 oncology providers and HERC staff to aid in the development of this proposal.

#### **Proposal and Methods:**

A new Antineoplastics preferred drug list (PDL) class was created and all applicable agents (whether previously in a PDL class or not) were added to the class.

This proposal to require PA encompasses any new start of an antineoplastic agent approved within the past 12 years. Drugs with an original FDA-approval date prior to January 2008, or subsequently approved new formulations of these older agents, are exempted from this criteria given the increased clinical experience with these agents.

The CMS Approval Date and National Drug Data File (NDDF) Add Date were utilized to identify antineoplastic drugs by unique generic name with a date for either field greater than or equal to 1/1/2008 for agents proposed to require PA. Any unique generic antineoplastic agents with any formulation identified with those parameters prior to 1/1/2008 are proposed to not require PA. A list of the medications proposed to require PA (n=85 unique generic name drugs) is provided in the proposed PA (**Appendix 1**) while the medications proposed to not require PA (n=108 unique generic name drugs) is provided in **Appendix 2**. The PA applies to pharmacy or physician administered drugs given in an outpatient setting and is not intended to apply to emergency or inpatient services.



**Covered Alternatives:**

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for treatment of an oncologic emergency (e.g., superior vena cava syndrome [ICD-10 I87.1] or spinal cord compression [ICD-10 G95.20]) administered in the emergency department?	<b>Yes:</b> Approve for length of therapy or 12 months, whichever is less.	<b>No:</b> Go to #3
3. Is the request for any continuation of therapy?	<b>Yes:</b> Approve for length of therapy or 12 months, whichever is less.	<b>No:</b> Go to #4
4. Is the diagnosis funded by OHP?	<b>Yes:</b> Go to #5	<b>No:</b> Pass to RPh. Deny; not funded by the OHP.
5. Is the indication FDA-approved for the requested drug?  <u>Note:</u> This includes all information required in the FDA-approved indication, including but not limited to the following as applicable: diagnosis, stage of cancer, biomarkers, place in therapy, and use as monotherapy or combination therapy.	<b>Yes:</b> Pass to RPh. Approve for length of therapy or 12 months, whichever is less.	<b>No:</b> Go to #6

<b>Approval Criteria</b>		
<p>6. Is the indication recommended by National Comprehensive Cancer Network (NCCN) Guidelines® for the requested drug?</p> <p><u>Note:</u> This includes all information required in the NCCN recommendation, including but not limited to the following as applicable: diagnosis, stage of cancer, biomarkers, place in therapy, and use as monotherapy or combination therapy.</p>	<p><b>Yes:</b> Pass to RPh. Approve for length of therapy or 12 months, whichever is less.</p>	<p><b>No:</b> Go to #7</p>
<p>7. Is there documentation based on chart notes that the patient is enrolled in a clinical trial to evaluate efficacy or safety of the requested drug?</p>	<p><b>Yes:</b> Pass to RPh. Deny; medical appropriateness.</p> <p>Note: The Oregon Health Authority is statutorily unable to cover experimental or investigational therapies.</p>	<p><b>No:</b> Go to #8</p>
<p>8. Is the request for a rare cancer which is not addressed by National Comprehensive Cancer Network (NCCN) Guidelines® and which has no FDA approved treatment options?</p>	<p><b>Yes:</b> Go to #9</p>	<p><b>No:</b> Pass to RPh. Deny; medical appropriateness.</p>
<p>9. All other diagnoses must be evaluated for evidence of clinical benefit.</p> <p>The prescriber must provide the following documentation:</p> <ul style="list-style-type: none"> <li>• medical literature or guidelines supporting use for the condition,</li> <li>• clinical chart notes documenting medical necessity, and</li> <li>• documented discussion with the patient about treatment goals, treatment prognosis and the side effects, and knowledge of the realistic expectations of treatment efficacy.</li> </ul> <p>RPh may use clinical judgement to approve drug for length of treatment or deny request based on documentation provided by prescriber. If new evidence is provided by the prescriber, please forward request to Oregon DMAP for consideration and potential modification of current PA criteria.</p>		

**Table 1. Oncology agents which apply to this policy**

<b>Generic Name</b>	<b>Brand Name</b>
abemaciclib	VERZENIO
abiraterone acet,submicronized	YONSA
abiraterone acetate	ZYTIGA
acalabrutinib	CALQUENCE
ado-trastuzumab emtansine	KADCYLA
afatinib dimaleate	GILOTRIF
alectinib HCl	ALECENSA
Alpelisib	PIQRAY
apalutamide	ERLEADA
asparaginase (Erwinia chrysan)	ERWINAZE
atezolizumab	TECENTRIQ
avapritinib	AYVAKIT
avelumab	BAVENCIO
axicabtagene ciloleucel	YESCARTA
axitinib	INLYTA
belinostat	BELEODAQ
bendamustine HCl	BENDAMUSTINE HCL
bendamustine HCl	BENDEKA
bendamustine HCl	TREANDA
binimetinib	MEKTOVI
blinatumomab	BLINCYTO
bosutinib	BOSULIF
brentuximab vedotin	ADCETRIS
brigatinib	ALUNBRIG
cabazitaxel	JEVTANA
cabozantinib s-malate	CABOMETYX
cabozantinib s-malate	COMETRIQ
Calaspargase pegol-mknl	ASPARLAS
carfilzomib	KYPROLIS
cemiplimab-rwlc	LIBTAYO
ceritinib	ZYKADIA
cobimetinib fumarate	COTELLIC
copanlisib di-HCl	ALIQOPA
crizotinib	XALKORI
dabrafenib mesylate	TAFINLAR

dacomitinib	VIZIMPRO
daratumumab	DARZALEX
Darolutamide	NUBEQA
degarelix acetate	FIRMAGON
dinutuximab	UNITUXIN
durvalumab	IMFINZI
duvelisib	COPIKTRA
elotuzumab	EMPLICITI
enasidenib mesylate	IDHIFA
encorafenib	BRAFTOVI
Enfortumab vedotin-ejfv	PADCEV
Entrectinib	ROZLYTREK
enzalutamide	XTANDI
erdafitinib	BALVERSA
eribulin mesylate	HALAVEN
everolimus	AFINITOR
everolimus	AFINITOR DISPERZ
fam-trastuzumab deruxtecan-nxki	ENHERTU
fedratinib	INREBIC
gilteritinib	XOSPATA
glasdegib	DAURISMO
ibrutinib	IMBRUVICA
idelalisib	ZYDELIG
ingenol mebutate	PICATO
inotuzumab ozogamicin	BESPONSA
ipilimumab	YERVOY
Isatuximab	SARCLISA
ivosidenib	TIBSOVO
ixazomib citrate	NINLARO
larotrectinib	VITRAKVI
lenvatinib mesylate	LENVIMA
lorlatinib	LORBRENA
Lutetium Lu 177 dotate	LUTATHERA
midostaurin	RYDAPT
moxetumomab pasudotox-tdfk	LUMOXITI
necitumumab	PORTRAZZA
neratinib maleate	NERLYNX
niraparib tosylate	ZEJULA

nivolumab	OPDIVO
obinutuzumab	GAZYVA
ofatumumab	ARZERRA
olaparib	LYNPARZA
olaratumab	LARTRUVO
omacetaxine mepesuccinate	SYNRIBO
osimertinib mesylate	TAGRISSE
palbociclib	IBRANCE
panobinostat lactate	FARYDAK
pazopanib HCl	VOTRIENT
pembrolizumab	KEYTRUDA
pertuzumab	PERJETA
Pexidartinib	TURALIO
Polatuzumab vedotin-piiq	POLIVY
pomalidomide	POMALYST
ponatinib HCl	ICLUSIG
pralatrexate	FOLOTYN
pemigatinib	PEMAZYRE
ramucirumab	CYRAMZA
regorafenib	STIVARGA
ribociclib succinate	KISQALI
ribociclib succinate/letrozole	KISQALI FEMARA CO-PACK
romidepsin	ISTODAX
romidepsin	ROMIDEPSIN
rucaparib camsylate	RUBRACA
ruxolitinib phosphate	JAKAFI
Sacitizumab govitecan-hziy	TRODELVY
Selinexor	XPOVIO
siltuximab	SYLVANT
sipuleucel-T/lactated ringers	PROVENGE
sonidegib phosphate	ODOMZO
Tagraxofusp-erzs	ELZONRIS
talimogene laherparepvec	IMLYGIC
talazoparib	TALZENNA
Tazemetostat	TAZVERIK
tisagenlecleucel	KYMRIAH
trabectedin	YONDELIS
trametinib dimethyl sulfoxide	MEKINIST

trifluridine/tipiracil HCl	LONSURF
Tucatinib	TUKYSA
vandetanib	CAPRELSA
vandetanib	VANDETANIB
vemurafenib	ZELBORAF
venetoclax	VENCLEXTA
venetoclax	VENCLEXTA STARTING PACK
vismodegib	ERIVEDGE
ziv-aflibercept	ZALTRAP
zanubrutinib	BRUKINSA

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*P&T/DUR Review: 6/2020 (JP)*  
*Implementation: TBD*

**Appendix 2. Antineoplastic Agents Proposed to Not Require Prior Authorization**

Generic Name	Brand Name
aldesleukin	PROLEUKIN
alemtuzumab	CAMPATH
alitretinoin	PANRETIN
altretamine	HEXALEN
aminolevulinic acid HCl	AMELUZ
aminolevulinic acid HCl	LEVULAN
anastrozole	ANASTROZOLE
anastrozole	ARIMIDEX
arsenic trioxide	TRISENOX
azacitidine	AZACITIDINE
azacitidine	VIDAZA
BCG live	BCG (TICE STRAIN)
BCG live	THERACYS
bexarotene	BEXAROTENE
bexarotene	TARGRETIN
bicalutamide	BICALUTAMIDE
bicalutamide	CASODEX
bleomycin sulfate	BLEO 15K
bleomycin sulfate	BLEOMYCIN SULFATE
bortezomib	BORTEZOMIB
bortezomib	VELCADE
busulfan	BUSULFAN
busulfan	BUSULFEX
busulfan	MYLERAN
capecitabine	CAPECITABINE
capecitabine	XELODA
carboplatin	CARBOPLATIN
carmustine	BICNU
carmustine in polifeprosan 20	GLIADEL
cetuximab	ERBITUX
chlorambucil	LEUKERAN
cisplatin	CISPLATIN
cladribine	CLADRIBINE
clofarabine	CLOFARABINE
clofarabine	CLOLAR

Generic Name	Brand Name
cyclophosphamide	CYCLOPHOSPHAMIDE
cyclophosphamide	NEOSAR
cytarabine	CYTARABINE
cytarabine/PF	CYTARABINE
dacarbazine	DACARBAZINE
dactinomycin	COSMEGEN
dactinomycin	DACTINOMYCIN
dasatinib	SPRYCEL
daunorubicin HCl	DAUNORUBICIN HCL
daunorubicin/cytarabine lipos	VYXEOS
decitabine	DACOGEN
decitabine	DECITABINE
docetaxel	DOCEFREZ
docetaxel	DOCETAXEL
docetaxel	TAXOTERE
doxorubicin HCl	ADRIAMYCIN
doxorubicin HCl	ADRIAMYCIN RDF
doxorubicin HCl	DOXORUBICIN HCL
doxorubicin HCl	RUBEX
doxorubicin HCl peg-liposomal	DOXIL
doxorubicin HCl peg-liposomal	DOXORUBICIN HCL LIPOSOME
doxorubicin HCl peg-liposomal	LIPODOX
doxorubicin HCl peg-liposomal	LIPODOX 50
epirubicin HCl	ELLEENCE
epirubicin HCl	EPIRUBICIN HCL
erlotinib HCl	TARCEVA
estramustine phosphate sodium	EMCYT
etoposide	ETOPOSIDE
etoposide	TOPOSAR
etoposide phosphate	ETOPOPHOS
exemestane	AROMASIN
exemestane	EXEMESTANE
floxuridine	FLOXURIDINE
fludarabine phosphate	FLUDARABINE PHOSPHATE
flurouracil	ADRUCIL

Generic Name	Brand Name
fluorouracil	CARAC
fluorouracil	EFUDEX
fluorouracil	FLUOROURACIL
fluorouracil	TOLAK
flutamide	FLUTAMIDE
fulvestrant	FASLODEX
gefitinib	IRESSA
gemcitabine HCl	GEMCITABINE HCL
gemcitabine HCl	GEMZAR
hydroxyurea	HYDREA
hydroxyurea	HYDROXYUREA
idarubicin HCl	IDAMYCIN PFS
idarubicin HCl	IDARUBICIN HCL
ifosfamide	IFEX
ifosfamide	IFOSFAMIDE
ifosfamide/mesna	IFOSFAMIDE-MESNA
imatinib mesylate	GLEEVEC
imatinib mesylate	IMATINIB MESYLATE
interferon alfa-2b, recomb.	INTRON A
interferon gamma-1b, recomb.	ACTIMMUNE
irinotecan HCl	CAMPTOSAR
irinotecan HCl	IRINOTECAN HCL
irinotecan liposomal	ONIVYDE
ixabepilone	IXEMPRA
kit Y-90/ibritumomab/h.albumin	ZEVALIN
lapatinib ditosylate	TYKERB
lenalidomide	REVLIMID
letrozole	FEMARA
letrozole	LETROZOLE
lomustine	GLEOSTINE
mechlorethamine HCl	MUSTARGEN
mechlorethamine HCl	VALCHLOR
megestrol acetate	MEGESTROL ACETATE
melphalan	ALKERAN
melphalan	MELPHALAN
melphalan HCl	ALKERAN
melphalan HCl	MELPHALAN HCL

Generic Name	Brand Name
melphalan HCl/betadex sbes	EVOMELA
mercaptopurine	MERCAPTOPYRINE
mercaptopurine	PURIXAN
methotrexate	XATMEP
methotrexate sodium	METHOTREXATE
methotrexate sodium	TREXALL
methotrexate sodium/PF	METHOTREXATE
methotrexate sodium/PF	METHOTREXATE SODIUM
mitomycin	MITOMYCIN
mitomycin	MUTAMYCIN
mitotane	LYSODREN
mitoxantrone HCl	MITOXANTRONE HCL
nelarabine	ARRANON
nilotinib HCl	TASIGNA
nilutamide	NILANDRON
nilutamide	NILUTAMIDE
oxaliplatin	OXALIPLATIN
paclitaxel	PACLITAXEL
paclitaxel protein-bound	ABRAXANE
panitumumab	VECTIBIX
pegaspargase	ONCASPARG
peginterferon alfa-2b	SYLATRON
pemetrexed disodium	ALIMTA
pentostatin	NIPENT
plicamycin	MITHRACIN
procarbazine HCl	MATULANE
rituximab/hyaluronidase, human	RITUXAN HYCELA
sorafenib tosylate	NEXAVAR
streptozocin	ZANOSAR
sunitinib malate	SUTENT
tamoxifen citrate	SOLTAMOX
tamoxifen citrate	TAMOXIFEN CITRATE
temozolomide	TEMODAR
temozolomide	TEMOZOLOMIDE
temsirolimus	TORISEL
teniposide	TENIPOSIDE
thioguanine	TABLOID

Generic Name	Brand Name
thiotepa	TEPADINA
thiotepa	THIOTEPA
topotecan HCl	HYCAMTIN
topotecan HCl	TOPOTECAN HCL
toremifene citrate	FARESTON
trastuzumab	HERCEPTIN
tretinoin	TRETINOIN
valrubicin	VALSTAR

Generic Name	Brand Name
vinblastine sulfate	VINBLASTINE SULFATE
vincristine sulfate	VINCASAR PFS
vincristine sulfate	VINCRISTINE SULFATE
vincristine sulfate liposomal	MARQIBO
vinorelbine tartrate	NAVELBINE
vinorelbine tartrate	VINORELBINE TARTRATE
vorinostat	ZOLINZA

## Drug Class Literature Scan: Hepatitis C Direct Acting Antivirals

**Date of Review:** June 2020

**Date of Last Review:** September 2019

**Literature Search:** 08/01/2019 – 02/25/2020

### **Current Status of PDL Class:**

See **Appendix 1**.

### **Conclusions:**

- There is low quality evidence that ledipasvir/sofosbuvir (LDV/SOF) results in sustained virologic response at 12 weeks after treatment (SVR12) of 98% (124/126) in pediatric patients ages 3 to 11 with chronic hepatitis C virus (HCV) genotype (GT) 1.
- There is low quality evidence that SOF plus ribavirin is efficacious in pediatric patients ages 3 to 11 with chronic HCV GT 2 or 3 infection with 98% (53/54) of patients achieving SVR12.
- There is low quality evidence that velpatasvir/sofosbuvir (VEL/SOF) results in SVR12 rates of 93% (66/71) in pediatric patients ages 6 to <12 years of age with chronic HCV GTs 1, 2, 3, and 4.
- There is low quality evidence of no serious treatment emergent adverse events in the pediatric population greater than 3 years of age and insufficient data to evaluate long-term safety.
- There is insufficient evidence to evaluate efficacy and safety of LDV/SOF or SOF in those with GT 4, 5 and 6, in pediatric patients with cirrhosis and in treatment experienced patients.
- There is no new comparative evidence evaluating long-term efficacy and safety of direct acting antivirals (DAAs) in chronic hepatitis C.

### **Recommendations:**

- Amend prior authorization criteria to include new FDA approved indications in pediatric patients.

### **Summary of Prior Reviews and Current Policy**

- There is low quality evidence that all of the direct acting antiviral (DAA) regimens are effective in achieving a SVR rate of greater than or equal to 90%. SVR rates differ between patients based on disease severity, genotype, and baseline NS5a resistant amino acid variants (RAVs).
- The regimens that have been studied in patients with cirrhosis include mostly Child-Pugh A and B. There are very limited data in Child-Pugh C.
- From the only comparative data available, there is low quality evidence that 12 weeks sofosbuvir/velpatasvir (SOF/VEL) may be modestly superior to 12 weeks SOF + ribavirin (RBV) in patients with genotype (GT) 2 (SVR 99% vs. 95%, respectively; absolute difference 5.2%; 95% CI, 0.2-10.3%; p=0.02). Treatment with 12 weeks of SOF/VEL may also be superior to 24 weeks of SOF + RBV in patients with GT 3 (SVR 95% vs. 80%; respectively; absolute difference 14.8%; 95% CI 9.6-20%; p<0.001).
- There are still several limitations in the current evidence for the treatment of CHC:

- There is still insufficient evidence for the optimal treatment of patients who have had a virologic failure to a previous NS5A or NS5B inhibitor. Risk of DAA resistance is a major concern in this population.
- There is still a lack of head-to-head trials for most DAA regimens. In some populations, data on DAAs are limited to open-label, uncontrolled, or historically controlled trials.
- Trials often exclude patients with chronic hepatitis B virus (HBV), HIV, cancer, hepatocellular carcinoma (HCC), decompensated cirrhosis, severe psychiatric, cardiac, pulmonary, or renal comorbidities, and severe alcohol or substance abuse. When decompensated cirrhosis is included, there are very little data in patients with Child-Pugh class C.
- There is no direct, randomized prospective evidence that treatment with antiviral therapy for CHC leads to improved long-term clinical outcomes in incidence of HCC, liver transplantation, or mortality.
- The Oregon Drug Use Review/Pharmacy & Therapeutics (P&T) Committee initially prioritized treatment for the fee-for-service population to patients in greatest need of treatment. Limited real-world experience and data, consideration for the number of patients waiting for treatment, limited provider expertise, and the limited number of alternative treatment options in cases of treatment resistance and patient comorbidities all played a role in prioritizing treatment. As more treatment options become available, real world experience increases, and the community standard evolves, the P&T Committee has expanded treatment in a step-wise fashion to patients with less severe disease.
- Current drug policies in place approve treatment for all patients with CHC, regardless of fibrosis severity or history of substance use disorder.

#### **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:**

After review, two systematic reviews were excluded due to poor quality.<sup>1,2</sup>

#### **New Guidelines:**

After review, one guideline update was excluded due to poor quality.<sup>3</sup>

#### **New Indications:**

1. The FDA approved sofosbuvir (SOF) (Solvadi®) and ledipasvir/sofosbuvir (LDV/SOF) (Harvoni®) for pediatric patients with HCV aged 3 years to younger than 12 years without cirrhosis or with compensated cirrhosis with GT 1, 4, 5 or 6. Prior to this, agents were approved for patients ages 12 years of age and older, and the only option for patients younger than 12 years was pegylated interferon plus ribavirin. Approval of LDV/SOF was based on a

multicenter, open-label, phase 2, non-comparative, single-arm study evaluating the safety and efficacy of LDV/SOF 45 mg/200 mg for 12 or 24 weeks in treatment-naïve (or interferon-experienced) children 3 to less than 12 years old with HCV genotype (GT) 1, 3 or 4 infection (n=126).<sup>4,5</sup> Patients were excluded if they had decompensated liver disease, acute hepatitis A, hepatitis B or human immunodeficiency virus (HIV), serum creatinine greater than 1.5 mg/dl, evidence of malignancy, significant cardiovascular, pulmonary or neurological disease, or psychiatric illness. All patients received 12 weeks of therapy, except interferon-experienced patients with cirrhosis, who received 24 weeks. Those with GT 3 and interferon treatment experience received ribavirin in addition to LDV/SOF. However, since LDV/SOF is not approved for treatment of GT 3, the efficacy in this group was not taken into consideration.<sup>6</sup> Although there were no pediatric patients with GT 5 or 6, FDA approved it based on pharmacokinetic data and efficacy data in adults.<sup>6</sup>

The majority of patients were treatment naïve, GT 1 (95%), without cirrhosis and were perinatally infected. Only two patients (ages 8 and 11) had compensated cirrhosis. In those ages 6 to 11, 99% (91/92) of patients achieved sustained virologic response at 12 weeks after treatment (SVR12).<sup>4</sup> In those ages 3 to less than 6, 97% (33/34) of patients achieved SVR12.<sup>5</sup> The most common adverse events in those 6 to 11 were headache (18%), fatigue (15%), vomiting (15%), and cough (15%).<sup>4</sup> The most common adverse events in those ages 3 to 6 were vomiting (24%), cough (21%), and pyrexia (21%).<sup>5</sup> Only one patient in either group discontinued treatment due to an adverse event (abnormal drug taste and vomiting).

Limitations to this study include lack of generalizability as there was only one patient with cirrhosis and only 4 patients had genotype 3 or 4. Additionally, there was no comparator, it was open-label and funding was provided by Gilead Sciences. Finally, many of the authors had significant conflicts of interest. Treatment options for pediatric patients who are DAA treatment experienced remains unknown.

LDV/SOF was also approved for pediatric patients with HCV GT 1 who have decompensated cirrhosis (Child-Pugh B or C) and for pediatric patients with HCV GT 1 or 4 infection who are liver transplant recipients without cirrhosis or with compensated cirrhosis. This approval was based on submitted pharmacokinetic data demonstrating similar LDF/SOF exposure as adults.<sup>6</sup>

2. SOF in combination with ribavirin was also FDA approved for pediatric patients 3 years of age and older with GT 2 or 3 chronic hepatitis C without cirrhosis or with compensated cirrhosis based on one phase 2 open-label study.<sup>7</sup> Treatment was administered for 12 weeks in those with GT 2 and 24 weeks in GT 3. A total of 54 patients were enrolled at 28 sites in Australia, Belgium, Germany, Italy, New Zealand, United Kingdom and the United States. Nineteen patients (35%) had GT 2 and 36 had GT 3 (67%). All but one patient was treatment naïve, and none of the patients had documented cirrhosis. All 41 of the patients aged 6 to less than 12 achieved SVR 12 (100%), and 12 of the 13 (92%) patients aged 3 to less than 6 years achieved SVR12.<sup>7</sup> Among patients aged 6 to less than 12 years, the most commonly reported adverse events were vomiting (32%) and headache (29%). Among the patients aged 3 to less than 6 years, the most common adverse events were vomiting (46%) and diarrhea (39%). Only one patient discontinued treatment due to an adverse event.

Limitations inherent to this study are similar to the above. Additionally, this was a small study including only GT 2 and 3 with minimal patients who were treatment experienced or who had cirrhosis. It remains unknown if those factors would impact SVR12 rates in this patient population. Additionally, this therapy requires the addition of weight-based ribavirin. Currently, SOF with ribavirin is the only FDA approved DAA regimen for children 3 through 11 years with GT 2 or 3 infection. However, recent clinical trials have evaluated SOF/VEL and glecaprevir/pibrentasvir (GLE/PIB) which would offer pangenotypic options without the need for ribavirin. Current HCV guidance panel recommends awaiting approval of these regimens unless there is an urgent or compelling need for immediate treatment in this subgroup.<sup>8</sup>

3. In November 2019, the FDA approved sofosbuvir-containing regimens, including LDV/SOF (Harvoni®), velpatasvir/sofosbuvir (VEL/SOF) (Epclusa®) and sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) (Vosevi®) for adults with severe renal impairment, including those who are on dialysis. None of these therapies require dosage adjustment for any degree of renal impairment. This approval was based on studies demonstrating efficacy and safety in LDV/SOF and VEL/SOF in patients with severe renal impairment.<sup>9,10</sup> Most patients (80%) experienced side effects similar to what is seen in other clinical trials, including fatigue, headache, nausea, vomiting and insomnia. There were no adverse effects associated with renal dysfunction observed in these short-term, single arm studies. The pharmacokinetics of VOX have not been studied in patients with patients with end stage renal disease.
4. In September 2019, the FDA approved GLE/PIB for those with compensated cirrhosis for 8 weeks. Previously, treatment in those with compensated cirrhosis required 12 weeks. Approval was based on the EXPEDITION-1 trial.<sup>11</sup> This was a single-arm, open-label phase IIIb trial conducted at 94 sites that evaluated patients 18 years of age or older, with chronic HCV GT 1-6 (n=343). Patients were HCV treatment-naïve and had documented cirrhosis. Patients with decompensated cirrhosis, HIV, and HBV were excluded from the trial. The majority of patients were male (63%), white (83%) and had GT 1 infection (67%). Overall, the SVR12 rate was 97.7% (335/343; 95% CI 96.1-99.3).<sup>11</sup> There was one patient with GT 3 who experienced relapse. Overall, 46% of patients experienced treatment-emergent adverse events. The most common were fatigue (9%), pruritis (8%), headache (8%), and nausea (6%). No patient discontinued treatment because of an adverse event. No liver-related toxicities or cases of drug-induced liver injury were observed. This study was open label, single arm and was funded and designed by AbbVie pharmaceuticals.
5. In March 2020, FDA approved VEL/SOF (Epclusa®) for children ages 6 and older or weighing at least 37 pounds with any of the six HCV genotypes without cirrhosis or with compensated cirrhosis, and in combination with ribavirin for those with decompensated cirrhosis.<sup>12</sup> Approval was based on an unpublished, phase 2, open-label study in adolescents and children. Following a pharmacokinetic lead in phase, 71 subjects 6 to 12 years of age with GT 1, 2, 3, or 4 HCV were treated with 12 weeks of VEL/SOF. Seventy six percent of individuals were GT 1 and the majority (94%) were treatment naïve. Overall, SVR rates were 93% (66/71).<sup>12</sup> The most common adverse events were fatigue and headache. Data remains unpublished<sup>13</sup> and results are not available on clinicaltrials.gov so further quality appraisal cannot be done at this time. The safety and efficacy in children < 6 years of age has not been established.

**New FDA Safety Alerts:**

None

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12. EPCLUSA (sofosbuvir and velpatasvir) prescribing information. Gilead Sciences, Inc. Foster City, CA. March 2020. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2020/208341s014lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208341s014lbl.pdf).
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14. Lok AS, Sulkowski MS, Kort JJ, et al. Efficacy of Glecaprevir and Pibrentasvir in Patients With Genotype 1 Hepatitis C Virus Infection With Treatment Failure After NS5A Inhibitor Plus Sofosbuvir Therapy. *Gastroenterology*. 2019;157(6):1506-1517.e1501.

**Appendix 1: Current Preferred Drug List**

<b>ROUTE</b>	<b>FORMULATION</b>	<b>BRAND</b>	<b>GENERIC</b>	<b>PDL</b>
ORAL	TABLET	MAVYRET	GLECAPREVIR/PIBRENTASVIR	Y
ORAL	TABLET	VOSEVI	SOFOSBUVIR/VELPTASVIR/VOXILAPREVIR	Y
ORAL	TABLET	EPCLUSA	SOFOSBUVIR/VELPATASVIR	Y
ORAL	TABLET	SOFOSBUVIR/VELPATASVIR	SOFOSBUVIR/VELPATASVIR	Y
ORAL	TABLET	DAKLINZA	DACLATASVIR	N
ORAL	TABLET	ZEPATIER	ELBASVIR/GRAZOPREVIR	N
ORAL	TABLET	HARVONI	LEDIPASVIR/SOFOSBUVIR	N
ORAL	TABLET	LEDIPASVIR/SOFOSBUVIR	LEDIPASVIR/SOFOSBUVIR	N
ORAL	TABLET DOSE PACK	VIEKIRA PAK	OMBITASVIR/PARITAPREVIR/RITONAVIR + DASABUVIR	N
ORAL	TABLET	SOVALDI	SOFOSBUVIR	N

## Appendix 2: New Comparative Clinical Trials

A total of 53 citations were manually reviewed from the initial literature search. After further review, 52 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining trial is summarized in the table below. Full abstracts are included in **Appendix 3**.

**Table 1. Description of Randomized Comparative Clinical Trials.**

Study	Comparison	Population	Primary Outcome	Results
Lok et al. <sup>14</sup> Phase 3b, open label RCT.	<u>Without Cirrhosis</u> GLE/PIB x 12 weeks (A) vs. GLE/PIB x 16 weeks (B)  <u>With Cirrhosis</u> GLE/PIB + RBV x 12 weeks (C) vs. GLE/PIB x 16 weeks (D)	Chronic HCV GT 1 treatment failure with SOF + NS5A inhibitor (n=177)	SVR12	A: 70/78 (90%; 95% CI 81-95%) B: 46/49 (94%; 95% CI 83-98%) C: 18/21 (86%; 95% CI 65-95%) D: 28/29 (97%; 95% CI 83-99%)

Abbreviations: GLE/PIB: glecaprevir/pibrentasvir; GT: genotype; HCV: hepatitis C virus; NS5A: non-structural protein 5A; RBV: ribavirin; RCT = randomized clinical trial; SOF: sofosbuvir; SVR12: sustained virologic response 12 weeks after treatment.

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### Appendix 3: Abstracts of Comparative Clinical Trials

**Lok AS, Sulkowski MS, Kort JJ, et al. Efficacy of Glecaprevir and Pibrentasvir in Patients With Genotype 1 Hepatitis C Virus Infection With Treatment Failure After NS5A Inhibitor Plus Sofosbuvir Therapy. Gastroenterology. 2019 Dec;157(6):1506-1517.e1. doi: 10.1053/j.gastro.2019.08.008. Epub 2019 Aug 8.**

#### BACKGROUND & AIMS:

Treatment options are limited for patients with hepatitis C (HCV) infection with treatment failure after sofosbuvir plus an NS5A inhibitor. There are some data for the efficacy of glecaprevir/pibrentasvir (G/P) in these patients. We performed a randomized trial of the safety and efficacy of 12 and 16 weeks of G/P, with or without ribavirin, in patients with HCV genotype 1 infection with treatment failure after sofosbuvir and an NS5A inhibitor.

#### METHODS:

We performed a phase 3b, open-label study of patients with chronic HCV genotype 1 infection who received previous treatment with sofosbuvir plus an NS5A inhibitor. Patients without cirrhosis were randomly assigned to groups that received G/P for 12 weeks (n = 78, group A) or 16 weeks (n = 49, group B). Patients with compensated cirrhosis were randomly assigned to groups that received G/P and ribavirin for 12 weeks (n = 21, group C) or G/P for 16 weeks (n = 29, group D). The primary end point was a sustained virologic response 12 weeks after treatment. Samples collected at baseline and at time of treatment failure were sequenced for resistance-associated substitutions in NS3 and NS5A.

#### RESULTS:

Of the 177 patients in the 4 groups, 81% were men, 79% had HCV genotype 1a infection, and 44% were black. Proportions of patients with sustained virologic response 12 weeks after treatment in groups A, B, C, and D were 90%, 94%, 86%, and 97%, respectively. The treatment failed in 13 (7.3%) patients with HCV genotype 1a infection, 6 (7.9%) in group A, 3 (6.1%) in group B, 3 (6.1%) in group C (6.1%), and 1 (3.4%) in group D. Most patients had baseline resistance-associated substitutions in NS5A. Treatment-emergent resistance-associated substitutions in NS3 and NS5A were observed in 9 and 10 patients with treatment failure, respectively. G/P was well tolerated. Ribavirin increased adverse events but did not increase efficacy.

#### CONCLUSIONS:

In a randomized study of patients with chronic HCV genotype 1 infection who received previous treatment with sofosbuvir plus an NS5A inhibitor, 16 weeks treatment with G/P produced sustained virologic response 12 weeks after treatment in >90% of patients, including those with compensated cirrhosis. ClinicalTrials.gov, Number: NCT03092375.

## Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to February 25, 2020

▼ Search History (33)				
<input type="checkbox"/>	# ▲	Searches	Results	Type
<input type="checkbox"/>	1	glecaprevir.mp.	193	Advanced
<input type="checkbox"/>	2	glecaprevir.mp.	193	Advanced
<input type="checkbox"/>	3	pibrentasvir.mp.	203	Advanced
<input type="checkbox"/>	4	mavyret.mp.	10	Advanced
<input type="checkbox"/>	5	sofosbuvir.mp. or SOFOSBUVIR/	2677	Advanced
<input type="checkbox"/>	6	velpatasvir.mp.	294	Advanced
<input type="checkbox"/>	7	voxilaprevir.mp.	91	Advanced
<input type="checkbox"/>	8	vosevi.mp.	11	Advanced
<input type="checkbox"/>	9	epclusa.mp.	16	Advanced
<input type="checkbox"/>	10	daclatasvir.mp.	1123	Advanced
<input type="checkbox"/>	11	daklinza.mp.	15	Advanced
<input type="checkbox"/>	12	technivie.mp.	5	Advanced
<input type="checkbox"/>	13	ombitasvir.mp.	511	Advanced
<input type="checkbox"/>	14	paritaprevir.mp.	501	Advanced
<input type="checkbox"/>	15	ritonavir.mp. or RITONAVIR/	6851	Advanced
<input type="checkbox"/>	16	dasabuvir.mp.	436	Advanced
<input type="checkbox"/>	17	simeprevir.mp. or SIMEPREVIR/	813	Advanced
<input type="checkbox"/>	18	ledipasvir.mp.	1034	Advanced
<input type="checkbox"/>	19	harvoni.mp.	69	Advanced
<input type="checkbox"/>	20	antiviral agents.mp. or Antiviral Agents/	80201	Advanced
<input type="checkbox"/>	21	direct acting antivirals.mp.	2662	Advanced
<input type="checkbox"/>	22	protease inhibitors.mp. or Protease Inhibitors/	43336	Advanced
<input type="checkbox"/>	23	ribavirin.mp. or RIBAVIRIN/	16681	Advanced
<input type="checkbox"/>	24	ns5a inhibitors.mp.	269	Advanced
<input type="checkbox"/>	25	ns5b inhibitor.mp.	108	Advanced

<input type="checkbox"/>	26	Hepatitis C, Chronic/ or Hepatitis C/	62849	Advanced
<input type="checkbox"/>	27	hepatocellular carcinoma.mp. or Carcinoma, Hepatocellular/	112599	Advanced
<input type="checkbox"/>	28	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	129678	Advanced
<input type="checkbox"/>	29	26 or 27	168501	Advanced
<input type="checkbox"/>	30	28 and 29	22229	Advanced
<input type="checkbox"/>	31	limit 30 to (english language and humans and yr="2019 -Current" and (clinical trial, phase iii or clinical trial, phase iv or comparative study or controlled clinical trial or meta analysis or practice guideline or randomized controlled trial or "systematic review"))	53	Advanced
<input type="checkbox"/>	32	from 31 keep 4, 11-12, 14, 16-17, 23, 27...	12	Advanced
<input type="checkbox"/>	33	from 32 keep 2, 7-9, 12	5	Advanced

## Hepatitis C Direct-Acting Antivirals

**Goals:**

- Approve use of cost-effective treatments supported by the medical evidence.
- Provide consistent patient evaluations across all hepatitis C treatments.
- Ensure appropriate patient regimen based on disease severity, genotype, and patient comorbidities.

**Length of Authorization:**

- 8-16 weeks

**Requires PA:**

- All direct-acting antivirals for treatment of Hepatitis C

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for treatment of chronic Hepatitis C infection (B18.2)?  Note: Accurate diagnosis of chronic hepatitis C infection typically includes positive detection of a viral load. Diagnosis should not rely solely on HCV antibody testing.	<b>Yes:</b> Go to #3	<b>No:</b> Pass to RPh. Deny; medical appropriateness.
3. Is expected survival from non-HCV-associated morbidities more than 1 year?	<b>Yes:</b> Go to #4	<b>No:</b> Pass to RPh. Deny; medical appropriateness.

## Approval Criteria

<p>4. Has <u>all</u> of the following pre-treatment testing been documented:</p> <ul style="list-style-type: none"> <li>a. Genotype testing in past 3 years is required if the patient has cirrhosis, <u>any</u> prior treatment experience, and if prescribed a regimen which is not pan-genotypic;</li> <li>b. Current HBV status of patient</li> <li>c. Pregnancy test in past 30 days for a woman of child-bearing age; <u>and</u></li> <li>d. History of previous HCV treatment and outcome</li> <li>e. Presence or absence of cirrhosis as clinically determined (e.g., clinical, laboratory, or radiologic evidence)?</li> </ul> <p>Note: Direct-acting antiviral agents can re-activate hepatitis B in some patients. Patients with history of HBV should be monitored carefully during and after treatment for flare-up of hepatitis. Prior to treatment with a DAA, all patients should be tested for HBsAG, HBsAb, and HBcAB status. HIV testing is also recommended, and modification of HIV or HCV treatment regimens may be needed if there are drug-drug interactions.</p>	<p><b>Yes:</b> Record results of each test and go to #5</p> <p>Note: If the patient has HIV or HBV co-infection, it is highly recommended that a specialist be consulted prior to treatment.</p> <p>Currently treatment is not recommended during pregnancy due to lack of safety and efficacy data</p>	<p><b>No:</b> Pass to RPh. Request updated testing.</p>
<p>5. Which regimen is requested?</p>	<p>Document and go to #6</p>	
<p>6. Does the patient have complications of cirrhosis (ascites, portal hypertension, hepatic encephalopathy, hepatocellular carcinoma, esophageal varices)?</p>	<p><b>Yes:</b> Go to #7</p>	<p><b>No:</b> Go to #8</p>
<p>7. Is the regimen prescribed by, OR is the patient in the process of establishing care with or in consultation with a hepatologist, gastroenterologist, or infectious disease specialist?</p>	<p><b>Yes:</b> Go to #8</p>	<p><b>No:</b> Pass to RPh. Deny; medical appropriateness.</p> <p>Recommend prescriber document referral to a specialist.</p>

<b>Approval Criteria</b>		
<p>8. Is there attestation that the patient and provider will comply with case management to promote the best possible outcome for the patient and adhere to monitoring requirements required by the Oregon Health Authority, including measuring and reporting of a post-treatment viral load?</p> <p>Case management includes assessment of treatment barriers and offer of patient support to mitigate potential barriers to regimen adherence as well as facilitation of SVR12 evaluation to assess treatment success.</p>	<b>Yes:</b> Go to #9	<b>No:</b> Pass to RPh. Deny; medical appropriateness.
<p>9. Is the prescribed drug:  a) Elbasvir/grazoprevir for GT 1a infection; <u>or</u>  b) Daclatasvir + sofosbuvir for GT 3 infection?</p>	<b>Yes:</b> Go to #10	<b>No:</b> Go to #11
<p>10. Has the patient had a baseline NS5a resistance test that documents a resistant variant to one of the agents in #16?</p> <p>Note: Baseline NS5A resistance testing is required.</p>	<b>Yes:</b> Pass to RPh; deny for appropriateness	<b>No:</b> Go to #11  Document test and result.
<p>11. Does the prescribed regimen include a NS3/4a protease inhibitor (elbasvir, glecaprevir, simeprevir, paritaprevir, voxilaprevir)?</p>	<b>Yes:</b> Go to #12	<b>No:</b> Go to #13
<p>12. Does the patient have moderate-severe hepatic impairment (Child-Pugh B or Child-Pugh C)?</p>	<b>Yes:</b> Pass to RPh; deny for appropriateness	<b>No:</b> Go to #13
<p>13. Is the prescribed regimen for the retreatment after failure of a DAA due to noncompliance or loss of follow-up?</p>	<b>Yes:</b> Pass to RPh; Deny and refer to medical director for review	<b>No:</b> Go to #14

## Approval Criteria

**14.** Is the prescribed drug regimen a recommended regimen based on the patient's genotype, age, treatment status (retreatment or treatment naïve) and cirrhosis status (see **Table 1 and Table 2**)?

**Yes:** Approve for 8-16 weeks based on duration of treatment indicated for approved regimen

**No:** Pass to RPh. Deny; medical appropriateness.

Note: Safety and efficacy of DAAs for children < 3 years of age have not been established

**Table 1: Recommended Treatment Regimens For Adults, and Adolescents 12 years of age and older with Chronic Hepatitis C virus.**

Treatment History	Cirrhosis Status	Recommended Regimen
<b>Genotype 1</b>		
DAA-Treatment naïve	Non-cirrhotic or compensated cirrhosis	SOF/VEL x 12 weeks G/P x 8 weeks
	Decompensated Cirrhosis	SOF/VEL + RBV x 12 week
Treatment experienced (Prior PEG/RBV)	Non-cirrhotic	SOF/VEL x 12 weeks G/P x 8 weeks
	Compensated cirrhosis	SOF/VEL x 12 weeks G/P x 12 weeks
Treatment Experienced (Prior sofosbuvir)	Non-cirrhotic or compensated cirrhosis	SOF/VEL x 12 weeks G/P x 12 weeks
Treatment Experienced (Prior NS3A/4A inhibitor)	Non-cirrhotic or compensated cirrhosis	SOF/VEL x 12 weeks G/P x 12 weeks
Treatment Experienced (prior NS5A-containing regimen)	Non-cirrhotic or compensated cirrhosis	G/P x 16 weeks
<b>Genotype 2</b>		
Naïve	Non-cirrhotic or compensated cirrhosis	SOF/VEL x 12 weeks G/P x 8 weeks
	Decompensated	SOF/VEL + RBV x 12 weeks
Treatment Experienced (prior PEG/RBV)	Non-cirrhotic	SOF/VEL x 12 weeks G/P x 8 weeks
	Compensated cirrhosis	SOF/VEL x 12 weeks

		G/P x 12 weeks
Treatment Experienced (SOF + RBV)	Non-cirrhotic or compensated cirrhosis	SOF/VEL x 12 weeks G/P x 12 weeks
Treatment Experienced (prior NS5A-containing regimen)	Non-cirrhotic or compensated cirrhosis	SOF/VEL/VOX x 12 weeks
<b>Genotype 3</b>		
Naïve	Non-cirrhotic or compensated cirrhosis	SOF/VEL X 12 weeks G/P x 8 weeks
	Decompensated Cirrhosis	SOF/VEL + RBV x 12 weeks
Treatment Experienced (prior PEG/RBV only)	Non-cirrhotic or compensated cirrhosis	SOF/VEL x 12 weeks G/P x 16 weeks
Treatment Experienced (SOF + RBV)	Non-cirrhotic or compensated cirrhosis	G/P x 16 weeks
Experienced (prior DAA-containing regimen, including NS5A)	Non-cirrhotic or compensated cirrhosis	SOF/VEL/VOX x 12 weeks
<b>Genotype 4</b>		
Treatment Naïve	Non-cirrhotic or compensated cirrhosis	SOF/VEL x 12 weeks G/P x 8 weeks
	Decompensated Cirrhosis	SOF/VEL + RBV x 12 week
Treatment Experienced (prior PEG/RBV only)	Non-cirrhotic	SOF/VEL x 12 weeks G/P x 8 weeks
	Compensated cirrhosis	SOF/VEL x 12 weeks G/P x 12 weeks
Treatment Experienced (prior DAA-containing regimen, including NS5A)	Non-cirrhotic or compensated cirrhosis	SOF/VEL/VOX x 12 weeks
<b>Genotype 5/6</b>		
Treatment Naïve	Non-cirrhotic or compensated cirrhosis	SOF/VEL x 12 weeks G/P x 8 weeks
	Decompensated cirrhosis	SOF/VEL + RBV x 12 weeks
Treatment Experienced (prior PEG-IFN/RBV only)	Non-cirrhotic	SOF/VEL x 12 weeks G/P x 8 weeks
	Compensated cirrhosis	SOF/VEL x 12 weeks G/P x 12 weeks
	Decompensated cirrhosis	SOF/VEL + RBV x 12 weeks
Experienced (prior DAA-containing regimen, including NS5A)	Non-cirrhotic or compensated cirrhosis	SOF/VEL/VOX x 12 weeks

Abbreviations: CTP = Child-Turcotte-Pugh; DAA = direct acting antiviral; EBV/GZR = elbasvir/grazoprevir; G/P = glecaprevir and pibrentasvir; PEG = pegylated interferon; RAV = resistance-associated variant; RBV = ribavirin; SOF = sofosbuvir; SOF/VEL = sofosbuvir/velpatasvir; SOF/VEL/VOX = sofosbuvir/velpatasvir/voxilaprevir

\*Evidence is insufficient if the addition of RBV may benefit subjects with GT3 and cirrhosis. If RBV is not used with regimen, then baseline RAV testing should be done prior to treatment to rule out the Y93 polymorphism.

^ Rarely, genotyping assays may indicate the presence of a mixed infection (e.g., genotypes 1a and 2). Treatment data for mixed genotypes with direct-acting antivirals are limited. However, in these cases, a pangenotypic regimen is appropriate.

Ribavirin-containing regimens are absolutely contraindicated in pregnant women and in the male partners of women who are pregnant. Documented use of two forms of birth control in patients and sex partners for whom a ribavirin containing regimen is chosen is required.

All regimens containing a protease inhibitor (elbasvir, glecaprevir, simeprevir, paritaprevir, voxilaprevir) should not be used in patients with moderate to severe hepatic impairment (CTP B and C).

There is limited data supporting DAA regimens in treatment- experienced patients with decompensated cirrhosis. These patients should be handled on a case by case basis with the patient, prescriber, and CCO or FFS medical director.

**Table 2: Recommended Treatment Regimens for children ages 3 - 12 years of age with Chronic Hepatitis C virus.**

Treatment History	Cirrhosis Status	Recommended Regimen
<b>Genotype 1</b>		
Treatment naïve or PEG/RBV Treatment Experienced	Non-cirrhotic or compensated cirrhosis	SOF/VEL x 12 weeks (≥ 6 years) LDV/SOF x 12 weeks (only for 3 - <6 years)
	Decompensated Cirrhosis	SOF/VEL + RBV x 12 week (≥ 6 years) LDV/SOF x 12 weeks + RBV (only for 3 - <6 years)
Treatment Experienced (Prior NS3A/4A inhibitor)	Non-cirrhotic	SOF/VEL x 12 weeks(≥ 6 years) LDV/SOF x 12 weeks (only for 3 - <6 years)
	Compensated cirrhosis	SOF/VEL x 12 weeks(≥ 6 years) LDV/SOF x 24 weeks (only for 3 - <6 years)
Note: Efficacy and safety not established in treatment experienced to other DAAs in this population		
<b>Genotype 2</b>		
Naïve	Non-cirrhotic or compensated cirrhosis	SOF/VEL x 12 weeks (≥ 6 years)
	Decompensated (safety and efficacy not established for < 6 years)	SOF/VEL + RBV x 12 weeks (≥ 6 years)
Treatment Experienced (prior PEG/RBV or NS3/4A)	Non-cirrhotic or compensated cirrhosis	SOF/VEL x 12 weeks(≥ 6 years)
	Decompensated (safety and efficacy not established for < 6 years)	SOF/VEL + RBV x 12 weeks (≥ 6 years)
Note: Efficacy and safety not established in treatment experienced to other DAAs in this population		
<b>Genotype 3</b>		

Naïve	Non-cirrhotic or compensated cirrhosis	SOF/VEL x 12 weeks (≥ 6 years)
	Decompensated (safety and efficacy not established for < 6 years)	SOF/VEL + RBV x 12 weeks (≥ 6 years)
Treatment Experienced (prior PEG/RBV or NS3/4A)  Note: Efficacy and safety not established in treatment experienced to other DAAs in this population	Non-cirrhotic or compensated cirrhosis	SOF/VEL x 12 weeks(≥ 6 years)
	Decompensated (safety and efficacy not established for < 6 years)	SOF/VEL + RBV x 12 weeks (≥ 6 years)
<b>Genotype 4, 5, or 6</b>		
Treatment naïve	Non-cirrhotic or compensated cirrhosis	SOF/VEL x 12 weeks (≥ 6 years) LDV/SOF x 12 weeks (only for 3 - <6 years)
	Decompensated Cirrhosis	SOF/VEL + RBV x 12 week
Treatment Experienced (prior PEG/RBV or NS3/4A)  Note: Efficacy and safety not established in treatment experienced to other DAAs in this population	Non-cirrhotic or compensated cirrhosis	SOF/VEL x 12 weeks (≥ 6 years) LDV/SOF x 12 weeks (only for 3 - <6 years)
	Decompensated cirrhosis	SOF/VEL + RBV x 12 week
Abbreviations: CTP = Child-Turcotte-Pugh; DAA = direct acting antiviral; EBV/GZR = elbasvir/grazoprevir; G/P = glecaprevir and pibrentasvir; PEG = pegylated interferon; RAV = resistance-associated variant; RBV = ribavirin; SOF = sofosbuvir; SOF/VEL = sofosbuvir/velpatasvir; SOF/VEL/VOX = sofosbuvir/velpatasvir/voxilaprevir		
^ Rarely, genotyping assays may indicate the presence of a mixed infection (e.g., genotypes 1a and 2). Treatment data for mixed genotypes with direct-acting antivirals are limited. However, in these cases, a pangenotypic regimen is appropriate.		
All regimens containing a protease inhibitor (elbasvir, glecaprevir, simeprevir, paritaprevir, voxilaprevir) should not be used in patients with moderate to severe hepatic impairment (CTP B and C).		
There is limited data supporting DAA regimens in treatment- experienced patients with decompensated cirrhosis. These patients should be handled on a case by case basis with the patient, prescriber, and CCO or FFS medical director.		

P&T Review: [6/20 \(MH\)](#); 9/19 (MH); 1/19; 11/18; 9/18; 1/18; 9/17; 9/16; 1/16; 5/15; 3/15; 1/15; 9/14; 1/14  
Implementation: [TBD](#); 1/1/20; 3/1/2019; 1/1/2019; 3/1/2018; 1/1/2018; 2/12/16; 4/15; 1/15

## Policy Evaluation: Hepatitis C: Direct-Acting Antivirals

### Research Questions:

- How has utilization of direct-acting antivirals (DAAs) changed over time as disease severity restrictions have been removed from the prior authorization (PA) criteria?
- Has there been an increase over time in the percentage of DAAs prescribed by primary care providers?
- Have patient characteristics and liver disease complications of those treated with DAAs changed over time with the opening up of treatment criteria?
- How many patients with chronic hepatitis C and concomitant alcohol and/or substance use disorder have been treated with a DAA?
- How many patients have been retreated with a DAA?

### Conclusions:

- Per member per month (PMPM) utilization of the DAAs has increased over time (**Figure 1**) and significant changes to the PA criteria in 2018 and 2019 resulted in an immediate increase in DAA utilization followed by stabilization.
- There was a clear shift of prescribing from specialty providers toward primary care providers after March 1, 2019. Approximately 62% of new DAA regimens were prescribed by primary care providers in the study group (March 2019-January 2020) compared to 47.3% in the control group (March 2019-February 2019).
- Revisions to the PA criteria in 2019 allowed for an increased percentage of DAA claims for patients with the absence of severe liver disease. There was a decrease in percentage of patients with comorbid compensated cirrhosis from 33.8% to 15.5% after revisions to the PA criteria. The percentage of those with comorbid decompensated cirrhosis was also reduced from 14.1% to 7.6% in the same time period.
- After policy changes in 2019, more patients with substance use disorder (SUD) were treated with a DAA, with 34.2% in the control group having a diagnosis of SUD compared to 48.7% in the study group.
- Retreatment rates with DAAs continue to be low (<2%) in all patients receiving DAAs.

### Recommendations:

- Maintain current prior authorization (PA) policy for DAAs and continue to monitor trends in utilization, changes in patient characteristics and barriers to patient access to treatment.
- Evaluate and follow up on fee-for-service (FFS) PA denials for potential patient outreach.

### Background:

Hepatitis C virus (HCV) infection is the most common blood born infection in the United States and has contributed substantially to hepatic related morbidity and mortality.<sup>1</sup> The true prevalence of chronic HCV infections is unknown due to the dynamic nature of the disease, but it is estimated that 2.4 million people in the United States were actively infected with HCV between 2013 and 2016.<sup>1</sup> Exact prevalence is difficult to determine because approximately 50% of people with HCV infection may be unaware of their diagnosis and another 15-20% will spontaneously clear acute HCV infection. In the United States, chronic HCV infection is

the leading cause of cirrhosis, liver failure, hepatocellular carcinoma (HCC), and liver transplants.<sup>2</sup> Chronic HCV is also the leading cause of death for blood born infections, surpassing human immunodeficiency virus (HIV) in 2007 with approximately 10-fold greater incidence of death compared to hepatitis B virus (HBV) related deaths.<sup>3</sup> The goals of treatment for HCV include prevention of these long-term complications of liver disease, eradication of HCV, and reduce transmission of HCV to others.<sup>4</sup>

For those without advanced liver disease, there has been an effort to increase prescribing by primary care providers. One large meta-analysis indicated that having primary care providers involved with managing HCV treatment led to similar and, in some cases, increased SVR rates and follow up.<sup>5</sup> Providing more access to HCV treatment via primary care providers has the potential to improve HCV related outcomes and reduce transmission in high-risk populations. Those at highest risk for transmitting and acquiring HCV infection are people who inject drugs.<sup>1</sup> This increased risk indicates the need to improve treatment availability for those with substance use disorder (SUD). A large meta-analysis conducted in 2018 indicated that those who inject drugs and those receiving medication assisted therapy (MAT) for SUD did not have significantly reduced SVR rates.<sup>6</sup>

Treatment for HCV has progressed significantly over the past decade. Only 55-60% of patients were able to achieve SVR with regimens prior to DAAs, and many patients experienced significant rates of adverse reactions to treatment. The development of second generation DAAs provided treatment options without the use of interferon or ribavirin that have fewer and more tolerable adverse effects. DAAs have the added benefit of being very effective in treating HCV, resulting in SVR for over 90% of patients in clinical trials. Additionally, duration of therapy has been shortened to 8-12 weeks in most patients with a number of regimens approved for treatment of all HCV genotypes. However, these medications come with a significant financial burden and definitive, long-term outcomes have yet to be established.

The Oregon Drug Use Review/Pharmacy & Therapeutics (P&T) Committee initially prioritized treatment for the fee-for-service population to patients in greatest need of treatment. Limited real-world experience and data, cost, consideration for the number of patients waiting for treatment, little provider expertise, and the limited number of alternative treatment options in cases of treatment resistance and patient comorbidities all played a role in prioritizing treatment. As more treatment options become available, real world experience increases, and the community standard evolves, the P&T Committee has expanded treatment in a step-wise fashion to patients with less severe disease (**Table 1**). Current drug policies in place approve treatment for patients with HCV regardless of disease severity.

The goal of this policy update is to determine how the most recent prior authorization changes outlined in **Table 1** have effected utilization of the DAAs and characteristics of patients receiving therapy.

**Table 1: Changes to PA criteria**

Implementation Date	Prior to 2018	January 2018	January 2019	March 2019
<b>Metavir Score Limitations</b>	Fibroscan <sup>®</sup> or FibroSure <sup>®</sup> with advanced fibrosis or cirrhosis ( <b>F3 or F4</b> ) OR APRI score > 1.5 or FIB-4 > 3.25 OR F2 (or APRI > 1.0) with HIV coinfection under treatment of specialist	<b>Confirmed F2</b> OR HIV co-infection OR extrahepatic manifestations of HCV infection AND if F3 or F4 required to be prescribed by specialist (< F2 no specialist needed)	<b>No changes</b>	<b>No fibrosis</b> or disease severity requirements. Prescribed by or in consultation with a specialist only for those with cirrhosis.

<b>Alcohol and Substance Use disorder limitations</b>	Patients required to be evaluated for alcohol and substance use disorder and was required to be enrolled in a treatment program or under care of an addiction specialist for approval	Patient actively abusing alcohol OR diagnosed with substance use disorder OR prescriber is aware of IV drug use THEN the patient must be enrolled in treatment program or under care of an addiction specialist for approval	Alcohol use and substance use disorder limitations removed from PA criteria	No changes
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**Table 2: Direct Acting Antiviral Regimens for Treatment of Chronic Hepatitis C Infection**

Drug Brand Name	Generic Name	Approved genotypes	Decompensated Cirrhosis	Mechanism of Action	Duration**	FDA Approval
<b>Epclusa</b> ®	Sofosbuvir/velpatasvir	HCV GT 1-6	GT 1-6 with RBV	NS5B inhibitor/NS5A inhibitor	12 weeks	June 2016
<b>Harvoni</b> ®	Ledipasvir/sofosbuvir	HCV GT 1, 4, 5, or 6	GT 1 with RBV	NS5A inhibitor/NS5B inhibitor	8-12 weeks	October 2014
<b>Mavyret</b> ®	Glecaprevir/pibrentasvir	HCV GT 1-6	Contraindicated	NS3/4A protease inhibitor/NS5B inhibitor	8-16 weeks	August 2017
<b>Vosevi</b> ®	Sofosbuvir/velpatasvir/voxilaprevir	HCV GT 1-6 TE	Contraindicated	NS5B inhibitor/NS5A inhibitor/NS3 protease inhibitor	12 weeks	July 2017
<b>Zepatier</b> ®	Elbasvir/grazoprevir	HCV GT 1 or 4	Contraindicated	NS3/4A protease inhibitor/NS5A inhibitor	12-16 weeks	January 2016

Abbreviations: TE = treatment experience; RBV = ribavirin; NS = nonstructural proteins; HCV = hepatitis C virus infection; GT = genotype

\*\*Duration typically 8-12 weeks for treatment naïve patients without decompensated cirrhosis. Duration of therapy extended for certain DAA-treatment experienced individuals and those with decompensated cirrhosis.

### Methods:

Overall utilization was evaluated over time by charting all paid CCO and FFS pharmacy claims for any DAA listed in **Table 2** from January 2015 through November 2019 (**Figure 1**). In order to look at utilization in more detail and evaluate the effects of removing all disease severity and abstinence prior authorization restrictions in March 2019, a pre and post-observational cohort was identified of patients newly started on DAA therapy. Patients with a paid FFS or CCO pharmacy claim for any DAA in **Table 2** from March 2018 through February 2019 (one year prior to the policy change) were defined as the control group, patients with claims from March 1, 2019 to January 31, 2020 were defined as the study group. Patients were included if they were newly started on a DAA, where new start is defined as no DAA in the year prior the earliest DAA claim in the respective period. Patients were excluded if they had less than 75% eligibility in the year prior to their index event (the date of the new start). Patients with Medicare Part D coverage as indicated by benefit packages of BMM, BMD, MND or MED were also excluded.

Baseline characteristics of age, gender, and race were assessed at the index event (IE). Patients were also categorized by IE prescriber type and if they were treatment experienced. Prescriber classifications were collected to determine what percentage of those prescribing DAAs were specialists compared to primary

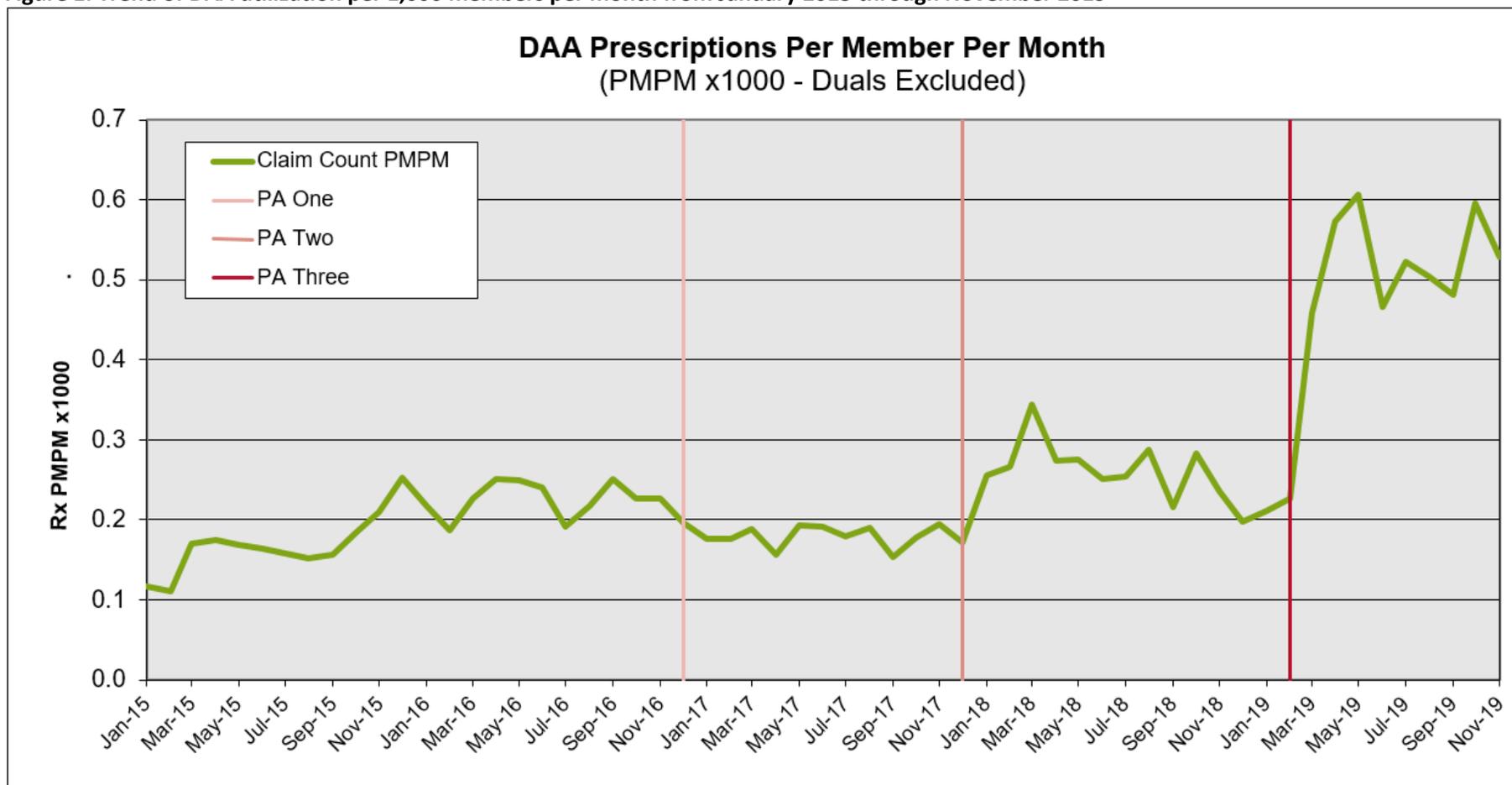
care providers before and after removing PA restrictions. The breakdown of each provider classification and how they were categorized is outlined in **Appendix 2**. Retreatment was defined as those with a second DAA course starting at least 12 weeks after the end of their initial DAA treatment. End of the initial treatment is defined as the first gap of greater than 2 weeks between subsequent DAA claims. Additionally, patients with substance use disorder, alcohol use disorder and liver disease complications were identified based on the diagnosis codes listed in **Appendix 3**.

Lastly, to describe changes in the proportion of patients with a diagnosis of HCV over time, the proportion all eligible patients in the Oregon Health Plan (OHP) during the pre- and post- periods with a diagnosis of hepatitis C since 2011 were collected (**Table 6**). The ICD-10 codes used to capture the diagnoses are included in **Appendix 3**. The percentage of these patients treated at any time since 2011 with a DAA is also included in **Table 6**.

**Results:**

**Figure 1** represents the utilization of DAAs per member per month (PMPM x 1000) from January 1, 2015 to November 30, 2019 in the Oregon Health Plan (OHP). DAA utilization increased after policy changes were implemented in January 2018 and March 2019. Of note, DAA claims peaked in May 2019 after PA criteria were modified to permit increased access to hepatitis C treatment. Since March 2019, DAA utilization has stabilized after the initial increase at approximately 0.5 to 0.6 claims PMPM x 1000. There was also a slight increase in DAA claims with revision of the PA restrictions in 2018, from 0.17 claims PMPM x 1000 in December 2017 to 0.25 claims PMPM x 1000 in January of 2018. This trend also stabilized.

Figure 1. Trend of DAA utilization per 1,000 members per month from January 2015 through November 2019



Demographics of FFS and CCO members in the control and study group are presented in **Table 3**. A total of 1,014 patients had claims for a DAA from March 2018 to February 2019 and 1,817 patients had claims for a DAA between March 2019 and February 2020. Race and gender distributions were similar between the two groups. There was a trend towards increased utilization in younger patients (those aged 18 to 34) after the 2019 PA criteria revisions as DAA claims increased from 8.1% in the control group to 18.1% in the study group. Similarly, claims for patients aged 55 years and greater decreased from 51.2% in the control group to 38.3% in the study group.

**Table 3. Demographics of patients receiving DAA treatment**

	March 2018-February 2019		March 2019-January 2020	
<b>Total Treated with DAA</b>	<b>N=1,014</b>		<b>N=1,817</b>	
<b>Average Age (min-max)</b>	52 (12-69)		48 (6-72)	
<b>&lt; 18 (%)</b>	1	0.1%	2	0.1%
<b>18-34 (%)</b>	82	8.1%	329	18.1%
<b>35-54 (%)</b>	412	40.6%	790	43.5%
<b>&gt;=55 (%)</b>	519	51.2%	696	38.3%
<b>Female</b>	451	44.5%	836	46.0%
<b>Race</b>				
<b>White</b>	595	58.7%	1,038	57.1%
<b>Black</b>	33	3.3%	47	2.6%
<b>Asian</b>	11	1.1%	20	1.1%
<b>Other</b>	69	6.8%	136	7.5%
<b>Unknown</b>	306	30.2%	576	31.7%

**Table 4** describes the comorbidities associated with patients starting a new DAA regimen in the control and study groups. Of the 1,014 treated in the control group, 33.8% had compensated cirrhosis and 14.1% had decompensated cirrhosis. In contrast, of the 1,817 patients that were treated in the study group, only 15.5% had associated compensated cirrhosis and 7.6% had associated decompensated cirrhosis. There was an increase in the percentage of those with a DAA claim having SUD from 34.2% in the control group to 49.7% in the study group. The rates of coexisting alcohol use disorder were similar in both the control and study group at 22.1% and 23.5%, respectively. There was a low percentage of subjects retreated with a DAA in both the study group (0.5%) and the control group (1.6%).

**Table 4. Comorbidities and complications of patients receiving DAA treatment**

	March 2018-February 2019		March 2019-January 2020	
<b>Total Treated with DAA</b>	<b>1,014</b>		<b>1,817</b>	
<b>Chronic Viral Hepatitis C</b>	1,009	99.5%	1,808	99.5%
<b>Compensated Cirrhosis</b>	343	33.8%	281	15.5%
<b>Decompensated Cirrhosis</b>	143	14.1%	139	7.6%
<b>Hepatocellular Carcinoma</b>	18	1.8%	19	1.0%
<b>Liver Transplant</b>	2	0.2%	1	0.1%
<b>Substance Use Disorder</b>	347	34.2%	903	49.7%
<b>Alcohol Use Disorder</b>	224	22.1%	427	23.5%
<b>Patients Retreated with DAA</b>	16	1.6%	9	0.5%

Provider trends are highlighted in **Table 5**. A higher percentage of primary care providers prescribed DAAs after the PA was updated in March 2019. Approximately 62% of new DAA regimens were prescribed by primary care providers in the study group compared to 47.3% in the control group. Full details about prescriber classifications are outlined in **Appendix 2**.

**Table 5. Prescriber Classifications**

	March 2018-February 2019		March 2019-January 2020	
<b>Total Treated with DAA</b>	<b>1,014</b>		<b>1,817</b>	
<b>Primary Care</b>	<b>480</b>	<b>47.3%</b>	<b>1,129</b>	<b>62.1%</b>
<b>Specialist</b>	<b>534</b>	<b>52.7%</b>	<b>688</b>	<b>37.9%</b>

**Table 6** presents the proportion of patients who possess a diagnosis of chronic hepatitis C infection within the entire eligible Oregon Medicaid population during the same two time periods using the analysis above. This table also reports the percentage of patients diagnosed with chronic hepatitis C infection who received new start DAA therapy. The percentage of patients diagnosed with chronic hepatitis C infection was similar between the two time periods, 2.5% prior to the latest PA revision and 2.4% after. The percentage of those who have received DAA was similar as well.

**Table 6. Proportion of Patients Diagnosed with Hepatitis C Enrolled and Treated with DAA**

	March 2018-February 2019		March 2019-January 2020	
<b>All Patients in Oregon Health Plan</b>	<b>989,304</b>		<b>1,001,445</b>	
<b>Patients with a diagnosis of hepatitis C</b>	<b>24,830</b>	<b>2.5%</b>	<b>24,367</b>	<b>2.4%</b>
<b>Patients Treated with DAAs</b>	<b>4,324</b>	<b>17.4%</b>	<b>4,388</b>	<b>18.0%</b>

**Discussion:**

This report shows trends in utilization of DAAs following PA criteria revisions in March 2019. As of March 2019, treatment is covered for all patients with HCV, regardless of disease severity. Immediately following implementation, DAA utilization almost doubled from 0.23 claims PMPM x 1000 in February 2019 to 0.46 claims PMPM x 1000 the following month. Utilization continued to increase through May 2019, and then stabilized over subsequent months. DAA utilization has increased over time due to a number of potential factors including decreasing costs, increased provider familiarity, provider education and screening efforts. Additionally, policy changes in 2019 allowed treatment for those patients not eligible under the previous criteria due to fibrosis restrictions. Data from **Table 4** exhibits that healthier patients with fewer liver disease complications were treated with DAAs after March 2019. Additionally, there were more patients with a diagnosis of SUD treated with a DAA.

There was also increased prescribing by primary care providers. Since primary care providers are more accessible to patients, this likely contributed to the increase in overall claims for DAAs. This is highlighted in **Table 5** as the amount of DAA prescriptions from primary care providers rose from 47.3% to 62.1% after the PA policy was revised. This increase could be due to increased familiarity, more safety and efficacy data, and ongoing training efforts such as the Oregon ECHO program. Reduction in percentage of patients treated with decompensated cirrhosis is also likely a contributing factor as guidelines still recommend these patients be treated by hepatologists or infectious disease specialists.<sup>7</sup>

Data from this report also describes a shift in age of patients with claims for DAAs. There was a decrease in percentage of patients that would be included in the hepatitis C screening birth cohort (1945-1965), or those over 55 years old. The decreased percentage of patients in this age group could be due to successful prior treatment. This group was more likely to have met previous PA requirements due to liver disease severity secondary to being infected with hepatitis C for a longer period of time. However, the total number of patients in this age demographic was similar between the two groups indicating that the revisions to the PA criteria allowed more access for younger patients to be treated. This is most prominently seen in the age 18-34 demographic as percentage of claims increased in this age group from 8.1% in the control group to 18.1% in the study group. The increase in DAA claims for those under 55 years old is likely related to this population being less likely to have progressive fibrosis. The removal of restrictions regarding substance use disorder is also presumably a contributing factor to expanding access to DAAs in this age demographic. The removal of restrictions regarding substance use disorder is also presumably a contributing factor to expanding access to DAAs in this age demographic. According to the CDC, the opioid epidemic has had the largest impact on patients aged 25-54 years old.<sup>8</sup> Intravenous drug use associated with the opioid epidemic has exposed many patients in this age group to acquisition of hepatitis C infection.<sup>7-9</sup>

Similar to what has been seen in other policy evaluations, the impact of this policy change had a significant impact on utilization. The overall utility of DAAs has increased substantially and DAAs are being prescribed more by primary care providers as anticipated. This policy update has also expanded access to a higher percentage of patients with concomitant substance use disorder, which is particularly critical as this is a high risk population for acquisition and transmission of hepatitis C infection. Despite the increased awareness of available agents and push for more hepatitis C testing, the percentage of Oregon Medicaid patients diagnosed with hepatitis C infection was similar before and after revision of the PA in March 2019. Additionally, the overall percentage of those with diagnosed hepatitis C infection that were treated with DAAs only slightly increased from 17.4% to 18.0%, indicating that there is still opportunity to expand utilization of DAAs.

**Limitations:**

Claims data was used for collection and analysis making it difficult to obtain specifics regarding comorbidities, length of treatment, treatment success, and retreatment of patients with DAAs. It is difficult to fully assess what re-treatment rates will be since a full year's worth of data after initial treatment in the study group was not yet available at the time of data collection. Use of claims data also impacts the total amount of patients with diagnosis of hepatitis C as analysis relies on ICD-10 codes. It is unclear if patients that have successfully treated for hepatitis C had the diagnosis removed or if diagnoses codes were omitted for those who have not yet received a prescription for treatment. A more prolonged time frame may indicate a more profound difference between the two groups. Information about other potential consequences or benefits from changes in PA criteria, such as impact on HCC, liver transplant, or mortality due to hepatic complications could not be included due to inherent limitations in claims data.

## Appendix 1. Direct Acting Antivirals Included in Search

Drug Brand Name	Generic Name	Indication	Mechanism of Action
<b>Epclusa</b> ®	Sofosbuvir/velpatasvir	HCV GT 1-6	NS5B inhibitor/NS5A inhibitor
<b>Harvoni</b> ®	Ledipasvir/sofosbuvir	HCV GT 1, 4, 5, or 6	NS5A inhibitor/NS5B inhibitor
<b>Mavyret</b> ®	Glecaprevir/pibrentasvir	HCV GT 1-6	NS3/4A protease inhibitor/NS5B inhibitor
<b>Vosevi</b> ®	Sofosbuvir/velpatasvir/voxilaprevir	HCV GT 1-6 TE with NS5A inhibitor	NS5B inhibitor/NS5A inhibitor/NS3 protease inhibitor
<b>Zepatier</b> ®	Elbasvir/grazoprevir	HCV GT 1 or 4 with RBV in those with RBV TE	NS3/4A protease inhibitor/NS5A inhibitor
<b>Epclusa</b> ®	Sofosbuvir/velpatasvir	HCV GT 1-6	NS5B inhibitor/NS5A inhibitor
<b>Harvoni</b> ®	Ledipasvir/sofosbuvir	HCV GT 1, 4, 5, or 6	NS5A inhibitor/NS5B inhibitor
<b>Olysio</b> ®	Simeprevir	HCV GT1 with sofosbuvir	NS3/4A protease inhibitor
<b>Sovaldi</b> ®	Sofosbuvir	HCV GT 2 or 3 with ribavirin or HCV GT 1 or 4 with ribavirin and peginterferon alfa	NS5B polymerase inhibitor
<b>Daklinza</b> ®	Daclatasvir		NS5A inhibitor
<b>Copegus</b> ®, <b>Rebetol</b> ®, <b>Ribasphere</b> ®	Ribavirin	HCV GT 1-4 with a DAA in circumstances listed above	Antiviral activity not fully understood. RBV increases the mutation frequency in genomes in several RNA viruses.
Abbreviations: TE = treatment experience; RBV = ribavirin; NS = nonstructural proteins; HCV = hepatitis C virus infection; GT = genotype			

**Appendix 2. DAAs Prescribed by Prescriber Classification**

	Before Updated Prior Authorization (Control Group)		After Updated Prior Authorization Criteria (Study Group)	
	N	(%)	N	(%)
<b>Primary Care Providers (Total)</b>	<b>480</b>	<b>47.3%</b>	<b>1,129</b>	<b>62.1%</b>
NURSE PRACTITIONER - FAMILY	131	12.9%	224	12.3%
PHYSICIAN-FAMILY MEDICINE	96	9.5%	204	11.2%
PHYSICIAN ASSISTANT - MEDICAL	92	9.1%	261	14.4%
PHYSICIAN-INTERNAL MEDICINE	92	9.1%	238	13.1%
PHYSICIAN ASSISTANT	33	3.3%	96	5.3%
NURSE PRACTITIONER	25	2.5%	58	3.2%
STUDENT IN AN ORGANIZED HEALTH CARE EDUCATION/TRAINING PROGRAM	4	0.4%	27	1.5%
PHARMACIST	2	0.2%	6	0.3%
NATUROPATH	2	0.2%	9	0.5%
NURSE PRACTITIONER - ADULT HEALTH	3	0.3%	6	0.3%
PHYSICIAN-GENERAL PRACTICE	0	0.0%	6	0.3%
<b>Specialty Providers (Total)</b>	<b>534</b>	<b>52.7%</b>	<b>688</b>	<b>37.9%</b>
PHYSICIAN-INTERNAL MEDICINE-GASTROENTEROLOGY	293	28.9%	328	18.1%
PHYSICIAN-INTERNAL MEDICINE-INFECTIOUS DISEASE	166	16.4%	292	16.1%
PHYSICIAN-INTERNAL MEDICINE-HEPATOLOGY	23	2.3%	23	1.3%
SPECIALIST	22	2.2%	18	1.0%
PHARMACIST - CLINICIAN (PHC) / CLINICAL PHARMACY SPECIALIST	21	2.1%	1	0.1%
PHYSICIAN-EMERGENCY MEDICINE	7	0.7%	8	0.4%
PHYSICIAN ASSISTANT - SURGICAL	1	0.1%	3	0.2%
PHYSICIAN-PEDIATRICS-PEDIATRIC GASTROENTEROLOGY	1	0.1%	1	0.1%
PHYSICIAN-PEDIATRICS	0	0.0%	5	0.3%
PHYSICIAN-ANESTHESIOLOGY	0	0.0%	1	0.1%
PHYSICIAN-INTERNAL MEDICINE-HEMATOLOGY&ONCOLOGY	0	0.0%	1	0.1%
PHYSICIAN-SURGERY-UROLOGY	0	0.0%	1	0.1%

### Appendix 3. Diagnosis Codes of Interest

Associated Diagnosis	ICD-10 Code
Chronic Hepatitis, Viral	
Chronic viral hepatitis C with or without hepatic coma and unspecified viral hepatitis C with or without hepatic coma	B1710, B1711, B182, B192x, Z2252
Cirrhosis	
Fibrosis and cirrhosis of the liver	K703x, K704x, K74x, K766
Compensated Cirrhosis	K7030, K740, K743, K744, K745, K7460, K7469
Decompensated Cirrhosis	G9340, G9341, G9349, I6783, I8500, I8501, I8510, I8511, K226, K228, K7210, K7290, K766, K767, R180, R188
Substance Use Disorder	
Opioid, sedative, hypnotic, anxiolytics, cocaine, stimulant, and other psychoactive substance related disorders	F11.x, F13.x, F14.x, F15.x, F19.x
Alcohol Use Disorder	
Alcohol abuse or dependence	F10.1x, F10.2x

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## Drug Class Review with New Drug Evaluations: Sickle Cell Disease

**Date of Review:** June 2020  
**Generic Name:** crizanlizumab  
voxelotor

**End Date of Literature Search:** 02/14/2020  
**Brand Name (Manufacturer):** Adakveo® (Novartis)  
Oxbryta™ (Global Blood Therapeutics)

**Purpose for Class Review:** The purpose of this update is to review drug therapy evidence for the treatment of sickle cell disease (SCD) and create a preferred drug list (PDL) class for this disease. Additionally, there are 2 new drugs that will be reviewed to determine place in therapy for SCD.

### Research Questions:

1. Is there high-quality comparative evidence demonstrating efficacy or effectiveness for therapies used for SCD?
2. Is there evidence for harms data for the therapies used for SCD?
3. Are there subgroups of patients based on demographics (e.g., age, race, sex, socio-economic factors) in which one therapy for SCD would be more effective or associated with less harm?
4. What is the evidence for efficacy and harms associated with voxelotor and how does this compare to other treatments for SCD?
5. What is the evidence for efficacy and harms associated with crizanlizumab and how does this compare to other treatments for SCD?

### Conclusions:

- Two clinical practice guidelines, one systematic review and 3 randomized controlled trials were identified that met inclusion criteria. Evidence from these sources revealed a paucity of high-quality evidence and limited treatment options for SCD.
- Hydroxyurea is appropriate for patients with SCD who experience pain crises 3 or more times in a 12-month period, and for infants 9-42 months of age, children, and adolescents to prevent complications of SCD (pain crisis frequency, duration, intensity, hospital admissions, vaso-occlusive crisis and opioid use) based on high-quality evidence.<sup>1</sup> Hydroxyurea should also be considered in adult patients who have sickle cell-related pain or sickle cell anemia that interferes with daily activities or quality of life and for patients with severe or recurrent acute coronary syndrome (moderate quality of evidence). These recommendations were reiterated in a clinical practice guideline by the National Heart, Lung and Blood Institute.<sup>2</sup>
- There is low quality of evidence from one trial of 230 patients that glutamine powder reduced the median number of pain crises more than placebo, with or without concomitant hydroxyurea therapy, median of 3 versus 4 over 48 weeks, respectively (P=0.005).<sup>3</sup>
- There is low quality of evidence from a small, double-blind, phase 3, randomized controlled trial lasting 72 weeks that more patients with SCD taking voxelotor had a hemoglobin response (defined by the investigators as an increase of more than 1.0 g/dL from baseline at week 24) compared to placebo.<sup>4</sup> There is insufficient evidence on the clinically meaningful change of hemoglobin levels. Patients on voxelotor 900 mg orally daily reported a 26% absolute increased response over placebo (NNT=4) and voxelotor 1500 mg orally daily had a 44% absolute increased response over placebo (NNT=3).<sup>4</sup> No statistically

significant difference in annualized rate of vasoocclusive events was found between either dose of voxelotor and placebo. Voxelotor was approved by the Food and Drug Administration (FDA) via an accelerated approval process. Additional evidence of clinical benefit is required by the FDA.

- There is low quality evidence from one phase 2 trial lasting 52 weeks that crizanlizumab 5 mg/kg intravenously (IV) reduced the annual number of pain crises in patients with SCD more than placebo by 1.35 less attacks per year (1.63 vs. 2.98; (95% confidence intervals not reported; P=0.01).<sup>5</sup>

#### **Recommendations:**

- Designate drugs for SCD as a PDL class.
- Add a hydroxyurea formulation as a preferred treatment option on the PDL.
- Designate voxelotor and crizanlizumab as non-preferred.
- Evaluate drug costs in the executive session.

#### **Background:**

Sickle cell disease is a common genetic disorder, with an estimated incidence of about 100,000 people in the United States (US).<sup>6</sup> Sickle cell disease is most prevalent in people of African, Mediterranean and Asian descent.<sup>6</sup> Sickle cell disease often presents in toddlers or young children and results in shortened life expectancy.<sup>7</sup> The cause of SCD is a genetic mutation of the hemoglobin structure that results in red blood cells with a sickle-shape which are inflexible and have increased the viscosity of blood.<sup>8</sup> Patients with SCD may either inherit two sickle genes (HbSS genotype) or inherit one sickle cell gene from one parent and different hemoglobin gene from the other parent (e.g., hemoglobin C,  $\beta$ -thalassemia).<sup>1</sup> The HbSS genotype is the most common genotype, occurring in 60-75% of SCD patients in the US.<sup>9</sup> Both the HbSS and HbS $\beta$ -thalassemia genotypes are referred to as sickle cell anemia (SCA).<sup>2</sup> Common characteristics of SCD are red blood cell hemolysis and vaso-occlusion, obstruction of blood flow. The blockage of small blood vessels prevents oxygen delivery to tissues causing severe pain.<sup>1</sup> Resulting comorbidities include blood clots, infection, organ damage, retinopathy, stroke and pain in the joint, extremities, back or chest.

Standard pharmacological treatment options for SCD are hydroxyurea, l-glutamine, and most recently, crizanlizumab and voxelotor. Hydroxyurea is the most utilized treatment for SCD and works by increasing fetal hemoglobin (HbF) concentrations. Infants are born with high levels of HbF, which gradually decreases with age to a normal adult level of HbF of less than 1% by age 2.<sup>10</sup> Studies have found that increasing levels of HbF help to prevent disorders of beta globin gene expression associated with SCD.<sup>10</sup> By increasing HbF concentrations, hydroxyurea has been found to increase nitric oxide metabolism (which is important in the synthesis of HbF) and reduction in red cell-endothelial interaction and erythrocyte density.<sup>1</sup> Improvement in these measures is associated with reduced pain crises (approximately 2.8 less pain crises annually compared to placebo), blood transfusions, and hospital admissions; however, there is no evidence that hydroxyurea improves mortality.<sup>1</sup> It is recommended to monitor blood counts for reduction in neutrophils and platelet in patients taking hydroxyurea. Hydroxyurea therapy has also been associated with teratogenic effects and reduced male fertility.<sup>1</sup> Glutamine was approved in 2017 for reduction in acute complications of SCD in adults and pediatric patients, 5 years of age and older.<sup>11</sup> While the exact mechanism of glutamine is unknown, it is thought to prevent oxidative damage to red blood cells, which are more susceptible in patients with SCD.<sup>11</sup> Non-pharmacological therapies for SCD include blood transfusions (to increase the oxygen capacity of blood), hemopoietic stem cell transplant and phlebotomy. Phlebotomy aids in reduction of HbS polymerization associated with SCD and subsequently decreases hospitalization duration and reduced Hb levels.<sup>12</sup>

Clinically meaningful outcomes for SCD include reduction in stroke, sickle cell pain crises, need for blood transfusion, end-organ damage, and mortality. Increases in hemoglobin concentrations are often measured, with increases associated with medication efficacy; however, specific HbF concentrations have not been correlated with subsequent outcome changes.<sup>7</sup>

Drug utilization in this class is very low and accounts for minimal expenditures. In 2019, 15 Oregon Health Plan fee-for-service patients had a diagnosis of SCD.

A summary of relevant drug information is available in **Appendix 1**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, warnings and precautions, including any Black Boxed Warnings and Risk Evaluation Mitigation Strategies.

**Table 1. Indications and Dosing.**

Drug Name (Manufacturer)	Indication(s)	Strength/Route	Dose and Frequency
Crizanlizumab-tmca Adakveo <sup>®13</sup> (Novartis)	Reduce the frequency of vasoocclusive crises in adults and pediatric patients aged 16 years and older with sickle cell disease	10 mg/mL solution via intravenous infusion	5 mg/kg over a period of 30 minutes on Week 0, Week 2 and every 4 weeks thereafter
Hydroxyurea Droxia <sup>®</sup> and Siklos <sup>®14,15</sup> (Bristol-Myers Squibb and Addmedica)	Reduce the frequency of painful crises and to reduce the need for blood transfusions in patients with sickle cell anemia with recurrent moderate to severe painful crises	200 mg, 300 mg and 400 mg capsules orally	15 mg/kg/day as a single daily dose for initial 12 weeks. Dose may be increased by 5mg/kg/day every 12 weeks until maximum tolerated dose or 35 mg/kg/day is reached
L-glutamine Endari <sup>™11</sup> (Emmaus Medical)	Reduce the acute complications of sickle cell disease in adult and pediatric patients 5 years of age and older	5 grams powder per packet orally in 8 oz. beverage or 4 oz. of food	5 grams to 15 grams twice daily based on body weight
Voxelotor Oxbryta <sup>™16</sup> (Global Blood Therapeutics)	Treatment of sickle cell disease in adults and pediatric patients 12 years of age and older	500 mg tablets orally	1500 mg once daily

**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 clinical practice guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

## Systematic Reviews:

### Cochrane – Hydroxyurea for Sickle Cell Disease

A 2017 Cochrane systematic review evaluated randomized and quasi-randomized controlled trials of hydroxyurea lasting at least one month.<sup>1</sup> Sixteen trials in children and adults with hemoglobin SS (HbSS), hemoglobin SC (HbSC), or hemoglobin S $\beta^0$ thalassemia (HbS $\beta^0$ thal) genotypes were identified. Most trials lasted 6-24 months.

Placebo-controlled comparisons provide moderate quality evidence that hydroxyurea decreases pain alteration (pain crisis frequency, duration, intensity, hospital admissions, vaso-occlusive crisis and opioid use) more than placebo (results were not pooled due to different measures of pain alterations).<sup>1</sup> Moderate evidence also suggests a decrease in life-threatening illnesses (acute chest syndrome and transfusions) in patients treated with hydroxyurea compared to placebo (results not pooled). However, risk of death was not statistically significantly different between hydroxyurea and placebo based on moderate evidence (RR 0.39; 95% CI, 0.08 to 1.96).<sup>1</sup> Fetal hemoglobin was increased in patients taking hydroxyurea compared to placebo (results not pooled). There was low quality evidence that hydroxyurea decreased pain recall more than placebo (MD 0.70; 95% CI, 0.11 to 1.29; P=0.02). Patients taking hydroxyurea reported a significant reduction in absolute neutrophil count compared to placebo (moderate evidence). Adverse events were similar between groups.

Hydroxyurea/phlebotomy was compared to transfusion/chelation in children and adults with increased risk of stroke (HbSS and HbS $\beta^0$ thal).<sup>1</sup> Phlebotomy aids in decreasing the viscosity of blood by reducing Hb levels and mean corpuscular Hb concentrations. The result of Hb reductions is reduced HbS polymerization, which is elevated in SCD.<sup>12</sup> There was moderate evidence of no difference between groups in the incidence of life-threatening illness (neurological events, hepatobiliary disease, or splenic sequestration); however, there were more acute chest syndrome, infections and parasite infestations in the hydroxyurea/phlebotomy group compared to transfusion/chelation. There was an increase in fetal hemoglobin in patients treated with hydroxyurea/phlebotomy compared to transfusion/chelation based on moderate evidence (results not pooled) and a decrease in absolute neutrophil count in patients treated with hydroxyurea/phlebotomy compared to transfusion/chelation.<sup>1</sup>

In conclusion, hydroxyurea was effective in children and adults for the outcome of pain and acute complications. The risk of life-threatening neurologic events was reduced in patients given hydroxyurea. Additional long-term data and the effect of hydroxyurea on fertility and reproduction are needed.

After review, 9 systematic reviews were excluded due to poor quality (e.g., 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).<sup>8,17-24</sup>

## Guidelines:

### National Heart, Lung and Blood Institute (NHLBI) – Evidence-Based Management of Sickle Cell Disease

In 2014, the NHLBI updated the guidelines on management of SCD.<sup>2</sup> The guidelines were supported by a systematic review of the literature, determining the quality of the evidence using Grading of Recommendations Assessment, Development and Evaluation (GRADE) and formulating recommendations ranging from “weak” to “strong”.<sup>2</sup> Hydroxyurea was the only available therapy for SCD at the time the guidelines were published. Recommendations for the use of hydroxyurea in SCD are presented in **Table 2**. Guidelines recommend the use of a prescribing monitoring protocol to be used in patients taking hydroxyurea, including blood counts and metabolic monitoring.

**Table 2. NHLBI Recommendations for the Use of Hydroxyurea in Patients with Sickle Cell Disease<sup>2</sup>**

Recommendation	Level of Evidence
1. Adults with SCA who have 3 or more sickle-cell moderate to severe pain crises in a 12-month period should be treated with hydroxyurea	Strong Recommendation, High-Quality of Evidence
2. Hydroxyurea should be given to adults with SCA who have sickle-cell associated pain that interferes with daily activities and quality of life	Strong Recommendation, Moderate-Quality of Evidence
3. Adults with SCA who have a history of severe and/or recurrent ACS, treat with hydroxyurea	Strong Recommendation, Moderate-Quality of Evidence
4. Hydroxyurea should be used as a treatment in adults with SCA who have severe symptomatic chronic anemia that interferes with daily activities or quality of life	Strong Recommendation, Moderate-Quality of Evidence
5. Infants (9 months of age and older), children and adolescents with SCA should be offered hydroxyurea regardless of clinical severity to minimize complications of SCD	Strong Recommendation, High-Quality of Evidence for ages 9-42 months Moderate Recommendation, Moderate-Quality of Evidence for children >42 months and adolescents
6. Hydroxyurea can be given to adults and children with SCD who have chronic kidney disease and are taking erythropoietin to improve anemia	Weak Recommendation, Low-Quality of Evidence
7. Hydroxyurea should be discontinued in women who are pregnant or breastfeeding	Moderate Recommendation, Low-Quality of Evidence

Abbreviations: ACS = acute coronary syndrome; SCA = sickle cell anemia ; SCD = sickle cell disease

American Society of Hematology – Cardiopulmonary and Kidney Disease 2019 Guidelines for Patients with Sickle Cell Disease

The American Society of Hematology updated its guidance in 2019 for patients with cardiopulmonary and renal complications related to SCD.<sup>25</sup> The evidence was evaluated using GRADE methodology and incorporated into recommendations. Sickle cell pharmacotherapy recommendations included only for the use of combination hydroxyurea and erythropoiesis-stimulating agents, up to a hemoglobin threshold of 10 g/dL, for children and adults with worsening anemia associated with chronic kidney disease (very low quality evidence).<sup>25</sup>

Additional Guidelines for Clinical Context:

After review, two guidelines were excluded due to poor quality.<sup>26,27</sup>

**Randomized Controlled Trials:**

A total of 234 citations were manually reviewed from the initial literature search. After further review, 233 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. Full abstracts are included in **Appendix 2**.

**Table 3. Description of Randomized Comparative Clinical Trials.**

Study	Comparison	Population	Primary Outcome	Results
Niihara, et al. <sup>3</sup>  (n=230)	L-glutamine 0.3 g/kg orally twice daily Vs. Placebo  48 weeks	Patients aged 5-58 years with SCA (HbSS or HbS $\beta^0$ -thalassemia) +/- stable dose of hydroxyurea and h/o $\geq 2$ pain crises in previous year	Incidence of pain crises among patients at 48 weeks	L-glutamine: 3.0 (median) (CI not reported) Placebo: 4.0 (median) (CI not reported) P=0.005  <i>L-glutamine reduced the number of pain crises more than placebo</i>

Abbreviations: HbS  $\beta^0$ -thalassemia = sickle  $\beta^0$ -thalassemia; HbSS = homozygous hemoglobin S; h/o = history of; SCA = sickle cell anemia; SCD = sickle cell disease

### **NEW DRUG EVALUATION: Voxelotor (Oxbryta™)**

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

#### **Clinical Efficacy:**

Voxelotor is a deoxygenated sickle hemoglobin (HbS) polymerization inhibitor which binds to hemoglobin to stabilize the oxygen state.<sup>16</sup> HbS polymerizes when deoxygenated which results in membrane damage and red-cell sickling. Voxelotor was approved via the accelerated approval pathway for the treatment of SCD in adult and pediatric patients 12 years of age and older.<sup>4</sup> Due to the accelerated approval, post-marketing studies to evaluate clinical benefit are required for voxelotor.

The HOPE trial was a phase 3, double-blind, placebo-controlled, 24-week, randomized trial used for the approval of voxelotor (see **Table 5**).<sup>4</sup> Patients were a median age of 25 years, 67% were African-American, predominately with HbSS genotype, and 65% were taking hydroxyurea.<sup>4</sup> Voxelotor 900 mg or 1500 mg once daily was compared to placebo in adults with sickle cell anemia (HbSS, sickle hemoglobin C disease or HbS $\beta^0$ thal). The primary endpoint was the percentage of patients who had a hemoglobin response (an increase of more than 1.0 g/dL from baseline) at week 24.<sup>4</sup>

Voxelotor demonstrated efficacy over placebo for both doses. Thirty-three percent of patients who received voxelotor 900 mg had a hemoglobin response compared to 51% who received voxelotor 1500 mg and 7% for the placebo group.<sup>4</sup> The absolute change compared to placebo was 26% for voxelotor 900 mg (NNT of 4) and 44% for voxelotor 1500 mg (NNT 3).<sup>4</sup> Attrition rates were 21-27% with voxelotor and 27% in patients treated with placebo.<sup>7</sup> There was no decrease in annualized vaso-occlusive events between groups.

Voxelotor was only studied in a small group of patients for a short duration. Only the surrogate endpoint of hemoglobin concentration was found to be significantly increased over placebo while a clinical endpoint of vaso-occlusive events was no different between groups. Additionally, most patients also received hydroxyurea which could also have a positive effect on hemoglobin concentrations. This study was also funded by the manufacturer. Additional evidence to

demonstrate long-term efficacy and clinical benefit in health outcomes is warranted. An efficacy trial involving the use of voxelotor in children with SCD is currently being conducted.

**Clinical Safety:**

The most common adverse events experienced amongst trial participants were headache, diarrhea, abdominal pain, nausea, rash, fatigue and pyrexia.<sup>7</sup> Serious drug adverse reactions were rare. Serious adverse events and adverse events related to discontinuation were similar between groups.<sup>4</sup>

**Comparative Endpoints:**

Clinically Meaningful Endpoints:

- 1) Stroke reduction
- 2) Reduction in vaso-occlusive crisis
- 3) Reduction in pain symptoms
- 4) Serious adverse events
- 5) Study withdrawal due to an adverse event

Primary Study Endpoint:

- 1) Hemoglobin response

**Table 4. Pharmacology and Pharmacokinetic Properties.**<sup>16</sup>

Parameter	
Mechanism of Action	Sickle hemoglobin polymerization inhibitor which prevents deoxygenation of hemoglobin (deoxygenated hemoglobin polymerizes and results in red-cell sickling and membrane damage)
Oral Bioavailability	Not described
Distribution and Protein Binding	338 L and Protein binding is 99.8%
Elimination	62.6% in the feces and 35.5% in the urine
Half-Life	35.5 hours
Metabolism	CYP3A4

Abbreviations:HbS = deoxygenated sickle hemoglobin

**Table 5. Voxelotor Comparative Evidence Table.**

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/N NT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Vichinsky, et al. <sup>4</sup>  (HOPE)	1. Voxelotor 900 mg PO once daily  2. Voxelotor 1500 mg PO once daily  3. Placebo	<u>Demographics:</u> Median Age: 25 y Female: 58% Concomitant hydroxyurea: 65% Baseline Hgb: 8.5 mg/dL	<u>ITT:</u> 1. 92 2. 90 3. 92  <u>PP:</u>	<u>Primary Endpoint:</u> % with Hgb response at week 24* 1. 30 (33%) (95% CI, 23 to 42) 2. 46 (51%) (95% CI, 41 to 61) 3. 6 (7%) (95% CI, 1 to 12)	         26%/ 4	Serious Adverse events: 1. 16 (17.4%) 2. 17 (19.3%) 3. 15 (16.5%)	NA for all	<b>Risk of Bias (low/high/unclear):</b> <u>Selection Bias:</u> Low. Patients were assigned in a 1:1:1 ratio. There were approximately 10% more women in the voxelotor 1500 mg group. <u>Performance Bias:</u> Low. Products were identical, preserving blinding. Blinding of participants and personnel were blinded.

<p>MC, PC, PG, DB, Phase 3, RCT</p>	<p>N = 274</p> <p>Screening period: 28-35 days</p> <p>Treatment period: 72 weeks (median follow-up of 39 weeks)</p>	<p>Patients with 1 vaso-occlusive crisis in the past 12 months: 42%</p> <p>Patients with 2-10 vaso-occlusive crises in the past 12 months: 58%</p> <p>HbSS genotype: 75%</p> <p><u>Key Inclusion Criteria:</u></p> <ul style="list-style-type: none"> <li>- Age 12-65 years</li> <li>- SCD diagnosis (homozygous Hgb S or Hgb Sβ-thalassemia)</li> <li>- Hgb 5.5 - 10.5 g/dL</li> <li>- 1-10 vasoocclusive crises in past 12 months</li> </ul> <p><u>Key Exclusion Criteria:</u></p> <ul style="list-style-type: none"> <li>- Pregnant/breastfeeding</li> <li>- Regular RBC transfusions</li> <li>- Hospitalization for sickle cell crisis or other vaso-occlusive event within 14 days</li> <li>- Hepatic dysfunction or severe renal dysfunction</li> <li>- Active infection</li> <li>- Cancer</li> </ul>	<p>1. 73</p> <p>2. 66</p> <p>3. 73</p> <p><u>Attrition:</u></p> <p>1. 19 (21%)</p> <p>2. 24 (27%)</p> <p>3. 19 (26%)</p>	<p>P&lt;0.001 for both voxelotor doses vs. placebo</p> <p><u>Secondary Endpoints:</u></p> <p>Change in Hgb from baseline to week 24:</p> <p>1. 0.6 g/dL (95% CI, 0.3 to 0.8)</p> <p>2. 1.1 g/dL (95% CI, 0.9 to 1.4)</p> <p>3. -0.1 g/dL (95% CI, -0.3 to 0.2)</p> <p>Voxelotor 900 mg vs. placebo: P&lt;0.05</p> <p>Voxelotor 1500 mg vs. placebo: P&lt;0.001</p>	<p>44%/ 3</p> <p>NA</p> <p>NA</p>	<p>Withdrawals due to Adverse Events:</p> <p>1. 5 (5.4%)</p> <p>2. 8 (9.1%)</p> <p>3. 4 (4.4%)</p> <p>Vaso-occlusive crisis (% not applicable):</p> <p>1. 183</p> <p>2. 179</p> <p>3. 219</p> <p>Headache:</p> <p>1. 14 (15%)</p> <p>2. 23 (26%)</p> <p>3. 20 (22%)</p>	<p><u>Detection Bias:</u> Unclear. Details on data analysis and maintaining blinding was not described.</p> <p><u>Attrition Bias:</u> High. Attrition 21-27%, with last observation carried forward imputation.</p> <p><u>Reporting Bias:</u> Low. Outcomes were reported as stated.</p> <p><u>Other Bias:</u> High. Funded by manufacturer.</p> <p><b>Applicability:</b></p> <p><u>Patient:</u> The majority of the included patients had a history of more than one vasoocclusive crises in the last year and those with the HbSS genotype.</p> <p><u>Intervention:</u> Voxelotor dose appropriate based on phase 2 trials.</p> <p><u>Comparator:</u> Placebo appropriate to establish efficacy of voxelotor.</p> <p><u>Outcomes:</u> Hemoglobin concentrations are a surrogate outcome and clinically significant changes have not been determined. The clinical significance of a 1 g/dL is unknown.</p> <p><u>Setting:</u> 60 centers in 12 countries (North America, Europe or other).</p>
<p><b>Abbreviations</b> [alphabetical order]: ARR = absolute risk reduction; CI = confidence interval; d = days; DB = double-blind; Hgb = hemoglobin; ITT = intention to treat; MC = multicenter; 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; NS = non-significant; PC = placebo controlled; PG = parallel group; PO = orally; PP = per protocol; RBC = red blood cell; RCT = randomized controlled trial; SCD = sickle cell disease; y = year.</p> <p>Key: * Hemoglobin response was defined as increase of more than 1.0 g/dL from baseline at week 24</p>							

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## **NEW DRUG EVALUATION: Crizanlizumab**

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

### **Clinical Efficacy:**

Crizanlizumab is a selectin blocker, a monoclonal antibody that binds to P-selectin. Up-regulation of P-selectin in endothelial cells and platelets are associated with cell interactions involved in vaso-occlusion and sickle cell pain crises. Crizanlizumab was approved, under the Breakthrough Therapy Designation, to reduce the frequency of vasoocclusive crises in adult and pediatric patients, ages 16 and older, with SCD.<sup>13</sup> Crizanlizumab is given by IV infusion over 30 minutes at week 0, week 2 and every 4 weeks thereafter. Approval was based on one phase 2 study (SUSTAIN) (See **Table 7**).<sup>5</sup>

The SUSTAIN trial was a double-blind, placebo-controlled, randomized clinical trial that evaluated crizanlizumab 2.5 mg/kg and 5 mg/kg versus placebo and given IV 14 times over 52 weeks.<sup>5</sup> A loading dose of 2 doses of crizanlizumab or placebo were given 2 weeks apart and then one dose every 4 weeks. The median age in the study was 28 years, 55% were female, and 71% had the HbSS genotype. The primary endpoint was the annualized rate of sickle cell-related pain crises (total number of crises multiplied by 365 and divided by [end date – date of randomization + 1]). A sickle cell pain crisis event was a pain episode due to a vasoocclusive event requiring treatment with opioids or nonsteroidal anti-inflammatory drugs. Additional crisis events included in the primary endpoint were acute chest syndrome, hepatic sequestration, splenic sequestration, and priapism; however, there were no events in any of the groups. Crizanlizumab 5 mg/kg was more effective in reducing the annualized rate of sickle cell pain crises compared to placebo (1.63 (95% CI, 0.0 to 3.97) vs. 2.98 (95% CI, 1.25 to 5.87); P=0.01).<sup>5</sup> Crizanlizumab 2.5 mg/kg was not statistically different from placebo in pain crises reduction. Reduction sickle cell -related pain crises was demonstrated in patients on the 5 mg/kg dose irrespective of hydroxyurea use or genotype.<sup>9</sup>

Attrition was high in all groups (32-37%) in the trial. The most common reason in all groups was withdrawal by subject. Multiple imputation was performed for dropouts using data from those patients who completed the study. Efficacy beyond 52 weeks has not been studied.

### **Clinical Safety:**

Adverse events that occurred in more than 3% of patients who received crizanlizumab versus placebo were nausea, arthralgia, back pain and pyrexia.<sup>13</sup> Serious adverse reactions occurred in 2 patients treated with crizanlizumab. Discontinuations due to adverse events occurred in 2.7% of crizanlizumab-treated patients compared to 5% of placebo treated patients.<sup>9</sup> There were no detectable antibody responses against crizanlizumab reported.<sup>5</sup>

### **Comparative Endpoints:**

Clinically Meaningful Endpoints:

- 1) Stroke reduction
- 2) Reduction in vaso-occlusive crisis
- 3) Reduction in pain symptoms
- 4) Serious adverse events
- 5) Study withdrawal due to an adverse event

Primary Study Endpoint:

- 1) Annual rate of sickle cell pain crisis

**Table 6. Pharmacology and Pharmacokinetic Properties.**

Parameter	
Mechanism of Action	Humanized IgG2 kappa monoclonal antibody that binds to P-selectin and blocks interactions with its ligands including P-selectin glycoprotein ligand 1.
Oral Bioavailability	Not applicable
Distribution and Protein Binding	4.26 L and Protein binding not described
Elimination	Not described
Half-Life	7.6 days
Metabolism	Expected to be metabolized into small peptides by catabolic pathways.

**Table 7. Crizanlizumab 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. Ataga, et al. <sup>5</sup>  (SUSTAIN)  MC, PC, DB, Phase 2, RCT	1. Crizanlizumab 2.5 mg/kg IV  2. Crizanlizumab 5 mg/kg IV  3. Placebo IV  All treatments given 14 times over 52 weeks	<u>Demographics:</u> Median Age: 28 y Female 55% Concomitant hydroxyurea: 63% Baseline HbSS Genotype: 71% Patients with a history of 2-4 pain crises in the previous 12 months at baseline: 63%  <u>Key Inclusion Criteria:</u> - Ages 16-65 years - sickle cell diagnosis (homozygous hgb S or hgb Sβ <sup>0</sup> -thalassemia, sickle hgb C disease, hgb	<u>ITT:</u> 1. 66 2. 67 3. 65  <u>PP:</u> 1. 45 2. 43 3. 41  <u>Attrition:</u> 1. 21 (32%) 2. 24 (36%) 3. 24 (37%)	<u>Primary Endpoint:</u> Annual rate of sickle cell pain crisis: 1. 2.01 (95% CI, 1.00 to 3.98) 2. 1.63 (95% CI, 0.00 to 3.97) 3. 2.98 (95% CI, 1.25 to 5.87)  Crizanlizumab 2.5 mg vs. placebo: TD -32.6% P=0.18  Crizanlizumab 5.0 mg vs. placebo: TD -45.3% P=0.01  <u>Secondary Endpoints:</u> Annual rate of days hospitalized: 1. 6.87 (95% CI, 0.00 to 18.00)	NS          NA	<u>Serious Adverse Events:</u> 1. 21 (33%) 2. 17 (26%) 3. 17 (27%)  <u>Pyrexia:</u> 1. 0 2. 2 (3%) 3. 1 (2%)  <u>Headache:</u> 1. 14 (22%) 2. 11 (17%) 3. 10 (16%)	NA for all	<b>Risk of Bias (low/high/unclear):</b> <u>Selection Bias:</u> Low. Randomized 1:1:1 centrally based on a block design with stratification based on number of pain crises in the preceding year and concomitant hydroxyurea use. Baseline characteristics were similar. <u>Performance Bias:</u> Low. Same administration to mask treatments. Compounding pharmacist was unblinded. All other sponsor and study contacts were blinded. <u>Detection Bias:</u> Low. Crises review committee, used for analysis of primary endpoint, was comprised of 3 independent hematologists. <u>Attrition Bias:</u> High. Attrition was high in all groups. Missing data will be imputed as the maximum rate of crises among study patients. <u>Reporting Bias:</u> Low. Outcome were reported as outlined. <u>Other Bias:</u> High. Study was funded by the manufacturer  <b>Applicability:</b>

	<p>Sβ<sup>+</sup>-thalassemia or other genotypes)  - 2-10 sickle cell-related pain crises in past 12 months  - hydroxyurea use past 6 months; stable dose for at least 3 months</p> <p><u>Key Exclusion Criteria:</u>  - Long-term red-cell transfusion therapy  - Hgb &lt;4.0 g/dL  - cancer  - Stroke in past 2 y</p>	<p>2. 4.00 (95% CI, 0.00 to 25.72)  3. 6.87 (95% CI, 0.00 to 28.30)</p> <p>Crizanlizumab 2.5 mg vs. placebo  P=0.84</p> <p>Crizanlizumab 5.0 mg vs. placebo  P=0.45</p>	<p><u>Patient:</u> The annual crisis rate was reduced by 34.6% in patients with the HbSS genotype and 50.5% with other genotypes, demonstrating effectiveness in both populations. Ninety-two percent of patients were African American with low applicability to other populations.  <u>Intervention:</u> Comparisons of two doses of crizanlizumab was appropriate based on a phase 1 trial.  <u>Comparator:</u> Placebo comparison appropriate for a phase 2 study in order to establish efficacy of drug.  <u>Outcomes:</u> Sickle cell pain crisis is a clinically meaningful endpoint. Actual number of pain crises would be helpful.  <u>Setting:</u> Sixty sites in 3 countries (151 patients from US sites).</p>
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**Abbreviations** [alphabetical order]: ARR = absolute risk reduction; CI = confidence interval; DB = double-blind; HgB = hemoglobin; HbSS = homozygous hemoglobin S; ITT = intention to treat; IV = intravenous; MC = multicenter; 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; PC = placebo controlled; PP = per protocol; TD = treatment difference; γ = years

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## Appendix 1: Specific Drug Information

**Table 8. Clinical Pharmacology and Pharmacokinetics.**

Drug Name	Mechanism of Action	Absorption	Metabolism/Excretion	Pharmacokinetics (mean)
Crizanlizumab <sup>13</sup>	Humanized IgG2 kappa monoclonal antibody that binds to P-selectin and blocks interactions with its ligands including P-selectin glycoprotein ligand 1.	NA	Expected to be metabolized into small peptides by catabolic pathways.	<ul style="list-style-type: none"> <li>• Half-life: 7.6 days</li> <li>• Cmax: 0.16 mg/mL</li> <li>• AUC<sub>last</sub>*: 33.6. mg/hr/mL</li> <li>• Vd: 4.26 L</li> </ul>
Hydroxyurea <sup>14,28</sup>	Exact mechanism unknown. Thought to inhibit DNA synthesis by acting as a	≥ 80%	60% hepatic metabolism and a minor pathway of degradation by urease found	<ul style="list-style-type: none"> <li>• Half-life: 1.7 hours (pediatrics) and 1.9-3.9 hours (adults)</li> <li>• Cmax: NA</li> </ul>

	ribonucleotide reductase inhibitor.		in intestinal bacteria. Urinary excretion accounted for 40%.	<ul style="list-style-type: none"> <li>• AUC: NA</li> <li>• Vd: 12 L (pediatrics) and 20 L (adults)</li> </ul>
L-glutamine <sup>11</sup>	Exact mechanism unknown. L-glutamine may improve the NAD (the pyridine nucleotides) redox potential in sickle RBCs through increasing availability of reduced glutathione and reducing damage in red blood cells.	NA	Various metabolic activities, including formation of glutamate and synthesis of proteins, nucleotides and amino sugars.	<ul style="list-style-type: none"> <li>• Half-life: 1 hour</li> <li>• Cmax: NA</li> <li>• AUC: NA</li> <li>• Vd: 200 mL/kg</li> </ul>
Voxelotor <sup>16</sup>	Hemoglobin S (HbS) polymerization inhibitor that binds to HbS with a 1:1 stoichiometry and exhibits preferential partitioning to RBCs.	Peak concentrations occur 6-18 hours after oral administration.	Metabolism is via Phase I (oxidation and reduction), Phase II (glucuronidation) and combination of Phase I and Phase II metabolism; primarily by CYP3A4.	<ul style="list-style-type: none"> <li>• Half-life: 35.5 hours</li> <li>• Cmax: 12.6 mcg/mL</li> <li>• AUC: 246 mcg·hr/mL</li> <li>• Vd: 338 L</li> </ul>

Abbreviations: AUC = area under the curve; Cmax = maximum concentration; NA – not available; RBCs = red blood cells; Vd = volume of distribution

Key: \* AUC<sub>last</sub> – the last measurement recorded

#### Use in Specific Populations:

- Crizanlizumab is approved for use in pediatric patients 16 years of age and older. Use in pregnant women and geriatric patients is insufficient.
- Glutamine is safe and effective for use in pediatric patients 5 years and older. There is limited data for use in geriatric patients but some evidence suggests a similar response as in younger individuals.
- Hydroxyurea has not been studied in pediatrics. Use in pregnant females is limited. A lower dose may be required for geriatric patients and renal function should be monitored, as risk of adverse events may be increased with impaired renal function.
- Voxelotor has been studied as safe and effective in pediatrics 12 years and older. There is insufficient evidence for use in geriatric patients and pregnant women.

#### Drug Safety:

Boxed Warnings: Droxia (hydroxyurea) capsules have a boxed warning for the risk of severe myelosuppression. Avoid use in patients with decreased bone marrow function. Cancer has also been reported in patients taking hydroxyurea and sun protection is advised.

Risk Evaluation Mitigation Strategy Programs: Not applicable.

Contraindications: There are no contraindications reported with glutamine or crizanlizumab. Voxelotor and hydroxyurea should not be used in patients with hypersensitivity to it or excipients.

**Table 9. Summary of Warnings and Precautions.**

<b>Warning/Precaution</b>	Crizanlizumab-tmca	Hydroxyurea	L-glutamine*	Voxelotor
Infusion-related reactions	X			
Interference with automated platelet counts	X			
Hypersensitivity Reactions				X
Interference with measurement of Hb subtypes				X
Myelosuppression		X		
Malignancies		X		
Embryo-fetal toxicity		X		
Vasculitic toxicity		X		
Avoid live vaccinations		X		
Avoid concomitant use of antiretroviral drugs		X		
Skin erythema in patients recently receiving radiation		X		

Key: \* No contraindications or precautions

## Appendix 2: Trial Abstracts

### A Phase 3 Trial of L-Glutamine in Sickle Cell Disease

Yutaka Niihara , Scott T Miller , Julie Kanter , Sophie Lanzkron , Wally R Smith , Lewis L Hsu , Victor R Gordeuk , Kusum Viswanathan , Sharada Sarnaik , Ifeyinwa Osunkwo , Edouard Guillaume , Swayam Sadanandan , Lance Sieger , Joseph L Lasky , Eduard H Panosyan , Osbourne A Blake , Tamara N New , Rita Bellevue , Lan T Tran , Rafael L Razon , Charles W Stark , Lynne D Neumayr , Elliott P Vichinsky , Investigators of the Phase 3 Trial of L-Glutamine in Sickle Cell Disease

**Background:** Oxidative stress contributes to the complex pathophysiology of sickle cell disease. Oral therapy with pharmaceutical-grade L-glutamine (USAN, glutamine) has been shown to increase the proportion of the reduced form of nicotinamide adenine dinucleotides in sickle cell erythrocytes, which probably reduces oxidative stress and could result in fewer episodes of sickle cell-related pain.

**Methods:** In a multicenter, randomized, placebo-controlled, double-blind, phase 3 trial, we tested the efficacy of pharmaceutical-grade L-glutamine (0.3 g per kilogram of body weight per dose) administered twice daily by mouth, as compared with placebo, in reducing the incidence of pain crises among patients with sickle cell anemia or sickle  $\beta^0$ -thalassemia and a history of two or more pain crises during the previous year. Patients who were receiving hydroxyurea at a dose that had been stable for at least 3 months before screening continued that therapy through the 48-week treatment period.

**Results:** A total of 230 patients (age range, 5 to 58 years; 53.9% female) were randomly assigned, in a 2:1 ratio, to receive L-glutamine (152 patients) or placebo (78 patients). The patients in the L-glutamine group had significantly fewer pain crises than those in the placebo group ( $P=0.005$ ), with a median of 3.0 in the L-glutamine group and 4.0 in the placebo group. Fewer hospitalizations occurred in the L-glutamine group than in the placebo group ( $P=0.005$ ), with a median of 2.0 in the L-glutamine group and 3.0 in the placebo group. Two thirds of the patients in both trial groups received concomitant hydroxyurea. Low-grade nausea, noncardiac chest pain, fatigue, and musculoskeletal pain occurred more frequently in the L-glutamine group than in the placebo group.

**Conclusions:** Among children and adults with sickle cell anemia, the median number of pain crises over 48 weeks was lower among those who received oral therapy with L-glutamine, administered alone or with hydroxyurea, than among those who received placebo, with or without hydroxyurea. (Funded by Emmaus Medical; ClinicalTrials.gov number, NCT01179217 .).

## Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to January 24, 2020

Search Strategy:

#	Searches	Results
1	hydroxyurea.mp. or Hydroxyurea/	12022
2	crizanlizumab.mp.	19
3	L-glutamine.mp. or Glutamine/	18572
4	voxelotor.mp.	16
5	1 or 2 or 3 or 4	30594
6	limit 5 to (english language and humans and yr="2000 -Current")	8461
7	limit 6 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	234

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**Appendix 4: Key Inclusion Criteria**

<b>Population</b>	Patients with sickle cell disease
<b>Intervention</b>	Therapies for sickle cell
<b>Comparator</b>	Placebo or active treatment
<b>Outcomes</b>	Hemoglobin response, blood transfusions, stroke, vasoocclusive crisis, hospitalizations, pain scores
<b>Timing</b>	Symptom onset
<b>Setting</b>	Outpatient

## Sickle Cell Anemia Drugs

**Goal(s):**

- Approve the use of drugs for sickle cell disease in a cost-effective manner based on evidence.

**Length of Authorization:**

- Up to 12 months

**Requires PA:**

- Non-preferred drugs

**Covered Alternatives:**

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	<b>Yes:</b> Go to #3	<b>No:</b> Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	<b>Yes:</b> Go to #4	<b>No:</b> Pass to RPh. Deny; not funded by the OHP.
4. Is this a renewal request for voxelotor or crizanlizumab?	<b>Yes:</b> Go to renewal criteria below.	<b>No:</b> Go to #5

Approval Criteria		
<p>5. Will the prescriber consider a change to a preferred product?</p> <p>Message:</p> <ul style="list-style-type: none"> <li>• Preferred products do not require a PA.</li> <li>• Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy &amp; Therapeutics Committee.</li> </ul>	<b>Yes:</b> Inform prescriber of covered alternatives in class.	<b>No:</b> Go to #6
6. Is the patient taking hydroxyurea, failed treatment (stable dose for at least 3 months) or have contraindications to hydroxyurea treatment?	<b>Yes:</b> Go to #7	<b>No:</b> Pass to RPh. Deny; Recommend trial of hydroxyurea (stable dose for 3 months)
7. Is the request for voxelotor and the patient is 12 years or older?	<b>Yes:</b> Go to #8	<b>No:</b> Go to #9
8. Does the patient have a hemoglobin level of 10.5 g/dL or less AND have a history of at least 1 pain crisis in the last 12 months?	<b>Yes:</b> Approve for up to 6 months. Record baseline hemoglobin value.	<b>No:</b> Pass to RPh. Deny; medical appropriateness
9. Is the request for crizanlizumab and the patient is 16 years or older?	<b>Yes:</b> Go to #10	<b>No:</b> Pass to RPh. Deny; medical appropriateness
10. Has the patient had at least 2 pain crises in the last 12 months?	<b>Yes:</b> Approve for up to 12 months	<b>No:</b> Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is the request for a renewal of voxelotor?	<b>Yes:</b> Go to #2	<b>No:</b> Go to #3
2. Has the patient had an increase in hemoglobin of at least 1 g/dL from baseline hemoglobin level since starting voxelotor?	<b>Yes:</b> Approve for 12 months.	<b>No:</b> Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
3. Is the request for a renewal of crizanlizumab?	<b>Yes:</b> Go to #4	<b>No:</b> See above for initial approval criteria.
4. Has the patient had a reduction in annual pain crises by at least 45%?	<b>Yes:</b> Approve for 12 months.	<b>No:</b> Pass to RPh. Deny; medical appropriateness.

P&T/DUR Review: 6/20 (KS)  
 Implementation: TBD

## Drug Class Update with New Drug Evaluation: Drugs for Duchenne Muscular Dystrophy

**Date of Review:** June 2020

**Generic Name:** golodirsen

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

### **Purpose for Class Update:**

To evaluate new comparative evidence for drugs for Duchenne muscular dystrophy (DMD) and place in therapy for golodirsen, an antisense RNA recently approved by the Food and Drug Administration (FDA).

### **Research Questions:**

1. What is the comparative efficacy or effectiveness of therapies for DMD?
2. What is the comparative safety of therapies for DMD?
3. Is golodirsen safer or more effective than currently available agents for the treatment of patients with DMD?
4. Are there any subgroups (based on age, gender, ethnicity, comorbidities, disease duration or severity) that would benefit or be harmed from drugs for DMD?

### **Conclusions:**

- There is no new comparative efficacy or safety data for eteplirsen or deflazacort. The required post-marketing study to verify and describe the clinical efficacy of eteplirsen has not yet been completed.
- There is insufficient evidence that use of golodirsen in patients with DMD mutations amenable to exon 53 skipping has any impact on symptoms, muscle or pulmonary function, quality of life, or disease progression.
- Golodirsen was approved based on an ongoing, single-arm, open-label, phase I/II trial which demonstrated a small improvement in dystrophin protein over 48 weeks (change of 0.9% of normal compared to baseline).<sup>1</sup> The functionality of the truncated dystrophin protein produced as a result of golodirsen treatment has not been determined and may vary depending on the type of inherited mutation. It is not known if improvement in dystrophin correlates to clinical outcomes, and there is no consensus on the minimum amount of dystrophin that may result in a clinical improvement.
- There is insufficient evidence regarding long-term safety of golodirsen. FDA labeling for golodirsen includes warnings for hypersensitivity reactions and renal adverse events.

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**Recommendations:**

- Update prior authorization criteria for DMD (**Appendix 5**).

**Summary of Prior Reviews and Current Policy**

- Therapies FDA approved for treatment of DMD (eteplirsen and deflazacort) were previously reviewed by the Pharmacy and Therapeutics (P&T) Committee in July 2017 and September 2019. A previous evaluation of deflazacort found insufficient evidence to evaluate differences in efficacy or safety between deflazacort and other corticosteroids for DMD or other conditions. Evidence was limited by small sample sizes, lack of reported methodology and outcomes, and inadequate data in a United States population of patients. Current evidence demonstrates no difference in functional outcomes for eteplirsen compared to placebo. Evidence is significantly limited by high risk of bias and small sample sizes.
- Prior authorization (PA) is currently required for eteplirsen and deflazacort to ensure medically appropriate use (see **Appendix 5**). Prednisone is available without PA.

**Background:**

Duchenne muscular dystrophy (DMD) is a rare X-linked genetic disorder caused by the absence of a functional dystrophin protein. DMD primarily affects males and is the most common type of muscular dystrophy with an estimated worldwide prevalence of 1.7 to 4.2 in 100,000 patients.<sup>2,3</sup> Patients with DMD experience progressive muscle deterioration leading to loss of ambulation and decreased muscle strength. Long-term complications include respiratory failure, dilated cardiomyopathy, arrhythmias, and increased risk for thrombotic events. In many patients, these complications can lead to wheelchair dependence by age 12 and death before the age of 20.<sup>2</sup>

There is currently no curative treatment for DMD, and therapy focuses on improving symptoms, enhancing quality of life, and decreasing disease progression. Guidelines from the American Academy of Neurology currently recommend initiation of corticosteroids, either deflazacort or prednisone, as first-line treatment for ambulatory children with a decline in motor function to delay loss of ambulation, preserve pulmonary function, and reduce risk of scoliosis.<sup>2,4</sup> Corticosteroids are often continued if patients become non-ambulatory, though the continued benefits are less clear with progressive disease.<sup>2</sup> Other non-pharmacological therapies which are often essential in disease management include physical therapy and use of support devices such as braces and wheelchairs.<sup>2</sup> As the disease progresses, mechanical ventilation and spinal surgery may be used to improve pulmonary function and decrease pain from scoliosis and vertebral fractures.<sup>2</sup>

Recent new therapies approved for DMD include eteplirsen and golodirsen. The goal of these therapies is to modify mRNA splicing and increase the amount of dystrophin protein in cells, thereby correcting the underlying disease process. Using this mechanism, a truncated dystrophin protein is formed. While preclinical animal studies indicate truncated dystrophin can be functional, the level of function associated with the truncated protein produced by golodirsen is unknown and may vary depending on the inherited mutation.<sup>5</sup> Eteplirsen was FDA approved in 2016 for DMD with mutations amenable to exon 51 skipping and golodirsen was FDA approved in 2019 for patients with mutations amenable to exon 53 skipping. Approximately 13% of patients with DMD are thought to have mutations amenable to exon 51 skipping.<sup>6</sup> There are currently 8 known mutations amenable to exon 53 skipping, which are thought to represent about 8% of the DMD population (approximately 1200 patients in the United States).<sup>7</sup> These therapies have been approved based on the surrogate marker of dystrophin protein. While eteplirsen and golodirsen have shown a slight increase in dystrophin (<1% of normal dystrophin levels), the clinical benefit of these therapies has not been established.<sup>8,9</sup> In the trial used for eteplirsen approval (n=12), there was no difference observed in the 6-minute walk test at 24 or 48 weeks compared to placebo. While subsequent follow-up studies have evaluated pulmonary, cardiac, and muscle function in this population, they are limited by their single-arm observational design, small sample size, and lack of comparator groups or comparison to historical control.<sup>10-12</sup> Confirmatory post-marketing, randomized trials have yet to be completed for eteplirsen.

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In untreated patients with DMD, documented dystrophin levels typically range from 0 to 0.4% of normal healthy patients.<sup>13</sup> Experts suggest that dystrophin levels less than 3% of normal are typically associated with a phenotype of DMD.<sup>13</sup> It is unclear whether increases in dystrophin protein level in patients with DMD correlate to clinical outcomes. Similarly, the minimum change in dystrophin level that may result in a clinical improvement has not been established. Some experts suggest that very minimal improvements in dystrophin level may constitute a beneficial change while others suggest that dystrophin levels at 10-20% of normal would likely correlate to clinically significant changes in muscle symptoms or function.<sup>13,14</sup> In patients with Becker muscular dystrophy, a less severe form of the muscular dystrophy, dystrophin protein levels are on average 80% of normal.<sup>13</sup>

Efficacy outcomes that are clinically important in patients with DMD include muscle strength, functional status, quality of life, disease progression, and mortality. Functional improvement is often evaluated using the 6-minute walk test (6MWT) and the North Star Ambulatory Assessment (NSAA) score. The 6MWT evaluates the distance a patient is able to walk in 6 minutes and evaluates both function and endurance.<sup>15</sup> In healthy children less than 7 years of age, the distance patients are able to walk is expected to remain stable or improve over time with estimated mean walk distances ranging from 500-700 meters.<sup>16-18</sup> The minimum clinically important difference in the 6MWT for patients with DMD is approximately 30 meters.<sup>15</sup> The NSAA evaluates 17 functional activities including standing, walking, standing up from a chair, standing on 1 leg, climbing/descending step, moving from lying to sitting, rising from the floor, jumping, hopping, and running.<sup>13</sup> Each item is evaluated on a 3-point scale with a total score ranging from 0 to 34. NSAA scores less than 16 are more often correlated with 6MWT of less than 300 meters and scores greater than 30 correlate moderately with 6MWT of more than 400 meters.<sup>19</sup> The NSAA is considered a more comprehensive measure of functional status compared to other functional assessments, but score is often very dependent on patient effort.<sup>13</sup> The minimum clinically important difference in NSAA score has not been determined. Other functional assessments include timed measures of rising from a sitting or supine position, 10-meter run/walking time, or time to climb 4 stairs.<sup>15</sup>

#### **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:**

No new high quality systematic reviews identified.

#### **New Guidelines:**

No new high quality guidelines were identified.

#### **New Formulations or Indications:**

Author: Servid

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No new formulations or indications were identified.

**New FDA Safety Alerts:**

No new safety alerts were identified.

**Randomized Controlled Trials:**

A total of 16 citations were manually reviewed from the initial literature search. None of the identified studies met quality inclusion criteria. Articles were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), outcome studied (e.g., non-clinical), or other key inclusion criteria in **Appendix 4**. The phase I/II, open-label extension trial evaluating efficacy of golodirsen was included in the new drug evaluation below as it was the primary trial used for FDA-approval.

**NEW DRUG EVALUATION:**

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

**Clinical Efficacy:**

Golodirsen is an antisense oligonucleotide which is designed to bind mRNA encoding the dystrophin protein resulting in altered mRNA splicing and restoration of the reading frame during protein formation to create a truncated dystrophin protein. Golodirsen was approved through the accelerated approval pathway based on a single, ongoing, phase I/II study which demonstrated changes in dystrophin over 48 weeks in 25 males with DMD and dystrophin mutations amenable to exon 53 skipping (described below in **Table 3**).<sup>1</sup> The study was divided into 2 parts. Part 1 was a randomized, double-blind, placebo-controlled, 12 week, dose titration study to evaluate the safety and pharmacokinetics of golodirsen. Patients completing part 1 of the study were enrolled in part 2 to evaluate efficacy and safety of golodirsen. Part 2 is an ongoing, single-arm, open-label extension study to evaluate efficacy and safety over 144 weeks (2.8 years).<sup>1</sup> The primary biologic outcome was dystrophin protein levels (evaluated by Western blot analysis) at 48 weeks, and the primary efficacy outcome was change in 6MWT at 144 weeks.<sup>1</sup> Relevant clinical secondary outcomes included pulmonary function tests. Currently only data for biologic outcomes at 48 weeks are published; data collection for efficacy outcomes was ongoing at the time of FDA approval.

Patients enrolled in the trial had DMD with mutations amenable to exon 53 skipping, were on average 8 years of age, were on corticosteroids for a mean duration of 3 years (minimum 6 months), had a mean percent predicted forced expiratory volume (ppFVC) of 93%, and had stable lung and cardiac function which was not expected to decline.<sup>1,7</sup> Efficacy of different doses was not evaluated in Part 1, and there was no dose-response or correlation observed with number of doses or duration of exposure and dystrophin production.<sup>1</sup> The highest dose (30 mg/kg weekly) was used for the Part 2 extension study. After 48 weeks of treatment, the mean dystrophin protein was 1.02% of normal (SD 1.03%) compared to an average value of 0.095% (SD 0.068%) at baseline (mean increase of 0.9% of normal).<sup>1</sup> Seven patients (28%) had a dystrophin level which remained below the lower limit of quantification for Western blot analysis (0.25% of normal) at 48 weeks.<sup>1,7</sup> Twelve patients (48%) had a dystrophin level that was less than 0.5% of normal, and only 2 patients had a dystrophin level over 2%.<sup>7</sup> This is similar to the change in dystrophin observed with eteplirsen treatment over 48 weeks in patients with mutations amenable to exon 51 skipping.<sup>9</sup> There is no consensus on what may constitute a clinically important change in dystrophin protein, as dystrophin levels have yet to be correlated to clinically relevant outcomes, and it is not clear if the truncated protein produced is functional. Additionally, the lack of a placebo group in Part 2 of the study increases risk

of biases and limits interpretation of these results as there is no method to evaluate changes in function, symptoms, or quality of life compared to the natural disease progression.

While data collection for functional outcomes is ongoing, available data was evaluated by the FDA. Functional outcomes up to 96 weeks are available for 24 of the 25 patients. Current data indicates a progressive decline in the average change in 6MWT from baseline of 26.1m at 48 weeks (n=25), 52.2 m at 72 weeks (n=25), 64.6 m at 96 weeks (n=24) and 86.1 m at 120 weeks (n=21).<sup>7</sup> Because there was no control group in this study, comparisons to placebo or no treatment are difficult to make, but FDA reviewers noted that this trend does not appear to be substantially different than natural history data for DMD patients.<sup>7</sup> In addition, there was no positive correlation between the change in 6MWT per year and change in dystrophin level (R=0.14), indicating that increases in a truncated dystrophin protein may not be an adequate surrogate marker for functional improvement.<sup>7</sup> Slight numerical declines were also noted in the average ppFVC ranging from 0.6% at 48 weeks (n=25) to 3.7% at 120 weeks (n=21).<sup>7</sup> The average decline in ppFVC for 18 patients at 144 weeks was -5.3%; data collection for the remaining patients is ongoing.<sup>7</sup> It is unclear if these changes represent clinically significant differences for DMD patients as baseline ppFVC was high (mean 93%) and pulmonary symptoms are not typically present until FVC declines further.

Like eteplirsen, the clinical benefit of golodirsen for DMD has not yet been established. Currently available data indicate no change in disease progression and only slight increases in dystrophin. In addition, use of a single-arm, open-label study design limits interpretation and increases risk of bias, particularly for functional outcomes such as the 6MWT or NSAA where performance is susceptible to expectation bias and coaching which significantly confounds the benefit observed in an open-label trial when compared to a historical disease progression. Significant exclusion criteria limit applicability in severe or progressive disease as patients were only included if they had stable cardiac and pulmonary function that, in the investigator's opinion, were unlikely to decompensate over the duration of the study. Additional data are needed to confirm clinical benefit. A confirmatory, placebo-controlled efficacy study evaluating golodirsen in patients with DMD and mutations amenable to exon 53 skipping is ongoing with planned enrollment of approximately 222 patients.<sup>7</sup>

### **Clinical Safety:**

Sixty patients with exposure to golodirsen from 2 ongoing studies were included in the safety analysis. Twenty-three patients were treated for more than 2 years, 23 were treated for more than 1 year and 11 were treated for less than 1 year.<sup>7</sup> Severe adverse events were infrequent and occurred in 2 patients with exposure to golodirsen (osteoporosis, fracture, and rhabdomyolysis) and in one patient randomized to placebo (fracture).<sup>7</sup> To date, none of the patients in ongoing trials have discontinued treatment due to adverse events.<sup>7</sup> While there were few serious adverse events documented in the study for golodirsen, the number of patients exposed to golodirsen is small and unlikely to detect rare adverse events. In the golodirsen clinical trial program and in safety reports at the time of FDA approval, there were no documented adverse events related to infection or renal problems. However, FDA reviewers noted risk for renal adverse events in pre-clinical animal studies and risk of infection associated with eteplirsen, a molecule with similar administration.<sup>7</sup>

In studies of rats, abnormalities in kidney function were observed including increases in blood urea nitrogen, creatinine, and included several instances of renal failure leading to death.<sup>7</sup> These adverse events were observed at doses which would result in plasma exposure of about 2.6 times higher than the FDA recommended dose.<sup>7</sup> Because golodirsen is primarily excreted unchanged in the urine, worsening renal function could lead to increased exposure and the potential for increased risk of renal adverse events.<sup>7</sup> Based on this information, FDA-labeling includes recommendations for renal monitoring. However, because patients with DMD typically have reduced muscle mass, serum creatinine levels are likely not an accurate measure of renal function for DMD patients.<sup>7</sup> Instead monitoring recommendations include baseline glomerular filtration rate via 24-hour urine collection, monthly assessments of proteinuria, and assessment of serum cystatin C every 3 months.<sup>8</sup> Reassessment of glomerular filtration rate is recommended if proteinuria or elevated serum cystatin C is observed.<sup>8</sup>

FDA reviewers also noted the potential for serious infection associated with indwelling IV ports, particularly in patients receiving chronic corticosteroids.<sup>7</sup> This concern was based on a review of post-marketing adverse event data for eteplirsen. Of the 469 patients known to be exposed to commercial eteplirsen, 11 cases (2.3%) of device infections, bacteremia, and sepsis had been reported through the FDA's Adverse Event Reporting System.<sup>7</sup> Because the FDA relies on voluntary reporting for clinicians, the exact incidence of these adverse events or occurrence for patients prescribed chronic corticosteroids is unknown. During clinical trials for golodirsen, there were no reports of serious infection. However, only half of patients treated with golodirsen (~30) received drug infusions via a central venous access port.<sup>7</sup>

Common adverse events are listed in **Table 1**. Of note, falls, fractures, accidents, and injuries were more common with treatment compared to placebo.<sup>7</sup> The exact etiology of these adverse events is unknown and confounding factors may include the degree of patient activity and DMD disease progression. In addition, hypersensitivity reactions requiring medical intervention were more common with golodirsen compared to placebo and labeling includes warnings for hypersensitivity reactions. The most common reactions included rash, pyrexia, pruritus, moderate urticaria, and dermatitis.<sup>7</sup>

Post-marketing requirements include studies to evaluate immune response to truncated dystrophin protein, carcinogenicity in animals, and a confirmatory trial evaluating clinical benefit.

**Table 1.** Adverse events occurring in more than 10% of patients and more common than placebo.<sup>7</sup>

Adverse Event	Golodirsen (%) N=60	Placebo (%) N=21
Headache	41	10
Pyrexia	41	14
Fall	29	19
Abdominal pain	27	10
Nasopharyngitis	27	14
Cough	27	19
Vomiting	27	19
Nausea	20	10
Administration site pain	17	0
Back pain	17	5
Pain	17	5
Dizziness	15	5
Ligament sprain	12	5

**Comparative Endpoints:**

Clinically Meaningful Endpoints:

- 1) Functional or symptom improvement (motor, pulmonary, or cardiovascular)
- 2) Quality of life
- 3) Disease progression

Primary Study Endpoints:

- 1) Biologic: Dystrophin protein levels at week 48
- 2) Efficacy: 6MWT at week 144

- 4) Serious adverse events
- 5) Study withdrawal due to an adverse event

**Table 2. Pharmacology and Pharmacokinetic Properties.<sup>8</sup>**

Parameter	
Mechanism of Action	Golodirsén binds to Exon 53 of the dystrophin pre-mRNA, resulting in exclusion of this exon during mRNA processing and producing an internally truncated dystrophin protein.
Oral Bioavailability	N/A
Distribution and Protein Binding	Volume of distribution of 668 mL/kg after 30 mg/kg dose Protein binding of 33-39%
Elimination	Excreted unchanged in the urine
Half-Life	3.4 hours (SD 0.6) with no apparent variation based on age or weight
Metabolism	N/A

Abbreviations: N/A = not applicable; SD = standard deviation

**Table 3. Comparative Evidence Table.**

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Frank, et al. <sup>1</sup>  FDA Clinical Review <sup>7</sup>  Phase I/II, DB, PC, RCT  NCT02310906	<b>Part 1:</b> 1. Golodirsen IV 4-30 mg/kg weekly 2. Placebo  12 weeks  In part 1, dose was initiated at 4 mg/kg for 2 weeks then patients were randomized to 10, 20 or 30 mg/kg doses followed by dose titration up to 30 mg/kg at 2 week intervals  <b>Part 2:</b> Patients from part 1 were enrolled in a Part 2 open-label phase of golodirsen IV 30 mg/kg weekly for 144 weeks. Part 2 is ongoing and enrolled an additional 13 patients.	<b>Demographics:</b> <b>Part 2:</b> - Age 8.2 y (SD 2.2) - Median BMI 18.1 kg/m <sup>2</sup> - 6MWT 403.7m (SD 56.7) - Corticosteroid duration of therapy: 36.8 months (SD 25.9) - Mean ppFVC 92.7% <sup>7</sup>  <b>Key Inclusion Criteria:</b> - 6-15 years of age - DMD diagnosis - Out-of-frame deletions amenable to exon 53 skipping - 6MWT ≥ 250 m - NSAA > 17 or Rise (Gowers) time < 7 seconds - LVEF ≥ 50% - QTc < 450 ms - ppFVC ≥ 50% - Stable oral corticosteroid for at least 24 weeks  <b>Key Exclusion Criteria:</b> - Nocturnal ventilator support - Other treatment which may affect muscle strength or function - Planned major surgery - Change in contracture treatment within 3 months - Other clinically significant illness which would interfere with participation	<b>ITT:</b> <b>Part 1:</b> 1. 8 2. 4  <b>Part 2:</b> 25  <b>Attrition:</b> <b>Part 1:</b> 1. 0 2. 0  <b>Part 2:</b> 2 (8%) <sup>7</sup>	<b>Primary Endpoint:</b> Change from baseline in dystrophin protein level at Week 48 (Western blot analysis)  Baseline: - Mean: 0.095% - SD: 0.068% - Range: 0.020-0.31% <b>Week 48:</b> - Mean: 1.019% - SD: 1.033% - Range: 0.09-4.30%  MD 0.92% (SD 1.01) <sup>7</sup>  6MWT at 144 weeks: NR  <b>Secondary Endpoints:</b> Pulmonary Function Tests: NR	NA for all	<b>Moderate treatment emergent AE:</b> 2  No serious AE or discontinuations due to AE were reported	NA for all	<b>Risk of Bias (low/high/unclear):</b> <b>Selection Bias:</b> HIGH. Part 1 randomized via IVRS, but baseline characteristics were unbalanced likely as a result of small sample size. Patients in golodirsen group were on average older, had longer time since diagnosis, and had longer duration of corticosteroid treatment. No randomization in Part 2. <b>Performance Bias:</b> HIGH. Part 1 double-blinded, but method of blinding for patients and providers was unspecified. 2 protocol violations regarding unblinding were noted. <sup>7</sup> Part 2 was open-label. Objective measures (e.g. dystrophin) are less likely to be affected by performance bias than functional measures (e.g., 6MWT). <b>Detection Bias:</b> LOW. Assessors of tissue analyses blinded to individual patients, time of biopsy, and treatment status via “blinding codes”. <b>Attrition Bias:</b> LOW. All patients completed initial 12 weeks. To date, 2 patients have withdrawn from the ongoing part 2 analysis for reasons unrelated to treatment. <b>Reporting Bias:</b> LOW. Biologic outcomes reported as specified. Data on functional outcomes was not reported as part 2 of the study remains ongoing. <b>Other Bias:</b> HIGH. Funding provided by Sarepta pharmaceuticals who was involved in data collection, analysis, interpretation, and writing the manuscript. Multiple authors (including the primary author) were employees and may own stock in the company.  <b>Applicability:</b> <b>Patient:</b> Included patients had stable cardiovascular disease, lung function ppFVC ≥50%, and baseline motor function tests which limits applicability to patients with more severe or progressive disease. <b>Intervention:</b> Dose appropriate for a phase I pharmacokinetic dose-finding trial. Efficacy of different doses was not evaluated. There was no correlation observed with number of doses or duration of exposure and dystrophin production. <b>Comparator:</b> Lack of control group after 12 weeks limits conclusions regarding efficacy of treatment or long-term safety. Placebo comparison would have been more useful. <b>Outcomes:</b> Functional outcomes not reported. Correlation of 6MWT or other functional outcomes with dystrophin levels is unclear. <b>Setting:</b> Centers in the United Kingdom, France, and Italy.

**Abbreviations** [alphabetical order]: 6MWT = 6 minute walk test; AE = adverse events; ARR = absolute risk reduction; CI = confidence interval; DB = double-blind; DMD = Duchenne muscular dystrophy; ITT = intention to treat; IV = intravenous; IVRS = interactive voice response system; LVEF = left ventricular ejection fraction; MD = mean difference; 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; NSAA = North Star Ambulatory Assessment; PC = placebo-controlled; PP = per protocol; ppFVC = percent predicted forced expiratory volume; RCT = randomized controlled trial; SD = standard deviation; y = years

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#### Appendix 1: Current Preferred Drug List

<u>Generic</u>	<u>Brand</u>	<u>Form</u>	<u>Route</u>
deflazacort	EMFLAZA	ORAL SUSP	PO
deflazacort	EMFLAZA	TABLET	PO
eteplirsen	EXONDYS-51	VIAL	IV
golodirsen	VYONDYS-53	VIAL	IV
prednisone	PREDNISONE INTENSOL	ORAL CONC	PO
prednisone	PREDNISONE	SOLUTION	PO
prednisone	PREDNISONE	TAB DS PK	PO
prednisone	PREDNISONE	TABLET	PO
prednisone	RAYOS	TABLET DR	PO

#### Appendix 2: Medline Search Strategy

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

1	eteplirsen.mp.	116
2	golodirsen.mp.	15
3	exp Glucocorticoids/	190109
4	deflazacort.mp.	569
5	Muscular Dystrophy, Duchenne/	5280
6	1 or 2 or 3 or 4	190528
7	5 and 6	318
8	limit 7 to (english language and humans)	266
9	limit 8 to yr="2019 -Current"	16

### Appendix 3: Prescribing Information Highlights

#### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VYONDYS 53™ safely and effectively. See full prescribing information for VYONDYS 53.

**VYONDYS 53 (golodirsen) injection, for intravenous use**  
**Initial U.S. Approval: 2019**

#### INDICATIONS AND USAGE

VYONDYS 53 is an antisense oligonucleotide indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 53 skipping. This indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with VYONDYS 53. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials. (1)

#### DOSAGE AND ADMINISTRATION

- Measure glomerular filtration rate prior to initiation (2.1)
- 30 milligrams per kilogram once weekly (2.2)
- Administer as an intravenous infusion over 35 to 60 minutes (2.2, 2.4)
- Dilution required prior to administration (2.3)

#### DOSAGE FORMS AND STRENGTHS

Injection: 100 mg/2 mL (50 mg/mL) in a single-dose vial (3)

#### CONTRAINDICATIONS

None (4)

#### WARNINGS AND PRECAUTIONS

- **Hypersensitivity Reactions:** Hypersensitivity reactions, including rash, pyrexia, pruritus, urticaria, dermatitis, and skin exfoliation have occurred in patients who were treated with VYONDYS 53. If a hypersensitivity reaction occurs, institute appropriate medical treatment and consider slowing the infusion or interrupting the VYONDYS 53 therapy. (2.3, 5.1)
- **Renal Toxicity:** Based on animal data, may cause renal toxicity. Renal function should be monitored; creatinine may not be a reliable measure of renal function in DMD patients. (5.2, 13.2)

#### ADVERSE REACTIONS

The most common adverse reactions (incidence  $\geq 20\%$  and higher than placebo) were headache, pyrexia, fall, abdominal pain, nasopharyngitis, cough, vomiting, and nausea. (6.1)

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

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2019

**Appendix 4: Key Inclusion Criteria**

<b>Population</b>	Duchenne Muscular Dystrophy
<b>Intervention</b>	Drugs in Appendix 1
<b>Comparator</b>	Drugs in Appendix 1
<b>Outcomes</b>	Symptoms (e.g., muscle, pulmonary, cardiac, etc), quality of life, functional improvement, disease progression, morbidity, or mortality
<b>Setting</b>	Outpatients

**Appendix 5: Prior Authorization Criteria**

**Drugs for Duchenne Muscular Dystrophy**

**Goal(s):**

- Encourage use of corticosteroids which have demonstrated long-term efficacy.
- Restrict use of eteplirsen, golodirsen, and deflazacort to patients with Duchenne Muscular Dystrophy and limit use of deflazacort to patients with contraindications or serious intolerance to other oral corticosteroids.

**Length of Authorization:**

- 6 months

**Requires PA:**

- ~~Targeted therapies for exon skipping~~
- ~~Eteplirsen (billed as a~~ (pharmacy or physician administered claims)
- Deflazacort

**Covered Alternatives:**

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

**Table 1. FDA Approved Indications**

<u>Drug</u>	<u>Indication</u>	<u>Examples of amenable mutations (list is not all inclusive)</u>
<u>eteplirsen (Exondys 51®)</u>	<u>Duchenne muscular dystrophy with mutations amenable to exon 51 skipping</u>	<u>Deletion of exons 43 to 50; 45 to 50; 47 to 50; 48 to 50; 49 to 50; 50; or 52</u>
<u>golodirsen (Vyondys 53®)</u>	<u>Duchenne muscular dystrophy with mutations amenable to exon 53 skipping</u>	<u>Deletion of exons 42 to 52; 45 to 52; 47 to 52; 48 to 52; 49 to 52; 50 to 52; 52; or 54 to 58</u>

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the drug being used to treat an OHP-funded condition <del>AND is the requested treatment funded by the OHP for that condition?</del>  <del>Note: Treatments referenced on an unfunded line of the prioritized list (<a href="http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Prioritized-List.aspx">http://www.oregon.gov/oha/HPA/CSI-HERC/Pages/Prioritized-List.aspx</a>) are not funded by the OHP.</del>	<b>Yes:</b> Go to #3	<b>No:</b> Pass to RPh. Deny; not funded by the OHP.
3. Is the request for treatment of Duchenne Muscular Dystrophy?	<b>Yes:</b> Go to #4	<b>No:</b> Pass to RPh. Deny; medical appropriateness.  Note: Eteplirsen, <a href="#">golodirsen</a> , and deflazacort are not indicated for other forms of muscular dystrophy or other diagnoses.
4. Is the request for continuation of <del>eteplirsen</del> -treatment?	<b>Yes:</b> Go to <b>Renewal Criteria</b>	<b>No:</b> Go to #5
5. Is the request for deflazacort?	<b>Yes:</b> Go to #6	<b>No:</b> Go to #9
6. Is the patient $\geq$ 2 years of age?	<b>Yes:</b> Go to #7	<b>No:</b> Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
<p>7. Has the patient received, or have contraindications to, all routine immunizations recommended for their age?</p> <p>Note: Routine vaccinations for patients at least 2 years of age typically include hepatitis B, hepatitis A, diphtheria, tetanus, pertussis, pneumococcal conjugate, inactivated poliovirus, influenza, and at least 2 doses of measles, mumps, rubella, and varicella.</p>	<p><b>Yes:</b> Go to #8</p> <p>Document physician attestation of immunization history.</p>	<p><b>No:</b> Pass to RPh. Deny; medical appropriateness.</p>
<p>8. Does the patient have a documented contraindication or intolerance to oral prednisone that is not expected to crossover to deflazacort?</p>	<p><b>Yes:</b> Approve for up to 12 months.</p> <p>Document contraindication or intolerance reaction.</p>	<p><b>No:</b> Pass to RPh. Deny; medical appropriateness.</p> <p>Recommend trial of <del>another oral corticosteroid</del> <u>prednisone</u>.</p>
<p>9. <del>Is the request for an FDA-approved indication (Table 1)? Does the patient have a diagnosis of Duchenne Muscular Dystrophy which is amenable to exon 51 skipping?</del></p> <p><del>Examples of amenable mutations include the following:</del></p> <ul style="list-style-type: none"> <li><del>• Deletion of exons 45 to 50</del></li> <li><del>• Deletion of exons 48 to 50</del></li> <li><del>• Deletion of exons 49 and 50</del></li> <li><del>• Deletion of exon 50 OR Deletion of exon 52</del></li> </ul>	<p><b>Yes:</b> Go to #10</p> <p>Document genetic testing.</p>	<p><b>No:</b> Pass to RPh, Deny; medical appropriateness.</p>
<p>10. <u>Is the request for golodirsen?</u></p>	<p><u><b>Yes:</b> Go to #11</u></p>	<p><u><b>No:</b> Go to #12</u></p>
<p>11. <u>Has the provider documented glomerular filtration rate as evaluated by a 24 hour urine collection within the past 3 months?</u></p>	<p><u><b>Yes:</b> Go to #12</u></p>	<p><u><b>No:</b> Pass to RPh. Deny; medical appropriateness.</u></p>

Approval Criteria		
41.12. Has the patient been on a stable dose of corticosteroid for at least 6 months <u>or have documented contraindication to steroids</u> ?	<b>Yes:</b> Go to #1 <u>34</u>	<b>No:</b> Pass to RPh. Deny; medical appropriateness.
42.13. Has baseline functional assessment been evaluated using a validated tool (e.g., the 6-minute walk test or North Star Ambulatory Assessment, etc)?	<b>Yes:</b> Document baseline functional assessment and approve for up to 6 months	<b>No:</b> Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. <u>Is the request for golodirsen?</u>	<b>Yes:</b> <u>Go to #2</u>	<b>No:</b> <u>Go to #3</u>
2. <u>Has the provider assessed renal function?</u>  <u>Recommended monitoring includes proteinuria monthly and serum cystatin C every three months. If results are abnormal, a 24H urine collection should be performed.</u>	<b>Yes:</b> <u>Go to #3</u>	<b>No:</b> <u>Pass to RPh, Deny; medical appropriateness.</u>
3. Has the patient's baseline functional status been maintained at or above baseline level or not declined more than expected given the natural disease progression?	<b>Yes:</b> <u>Go to #4</u> <u>Approve for up to 6 months</u>  Document functional status <u>and provider attestation.</u>	<b>No:</b> Pass to RPh, Deny; medical appropriateness.
4. <u>Is there documentation based on chart notes of any serious adverse events related to treatment (e.g., acute kidney injury, infections, etc.)?</u>	<b>Yes:</b> <u>Go to #5</u>	<b>No:</b> <u>Approve for up to 6 months</u>

## Renewal Criteria

5. Has the adverse event been reported to the FDA Adverse Event Reporting System (FAERS)?

**Yes:** Approve for up to 6 months

Document provider attestation

**No:** Pass to RPh, Deny; medical appropriateness.

*P&T/DUR Review:* 6/20: 09/19; 11/17; 07/17 (SS)  
*Implementation:* TBD: 11/1/19; 1/1/18; 9/1/17

# Dose Consolidation

June 4<sup>th</sup>, 2020

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**Oregon State**  
University

# Introduction

- Antipsychotics consistently an area of highest budget cost
- Many products have fixed cost (“flat priced”) across the range of strengths
- Patients may take multiple daily doses as they titrate up therapy and are never consolidated once a stable dose is obtained
- Goal: cost saving and reduction of tablet burden

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

Mental health medications account for large proportion of Fee For Service (FFS) medication expenditures.

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	LATUDA	Antipsychotics, 2nd Gen	\$5,882,372	16.2%	4,951	\$1,188	Y
2	INVEGA SUSTENNA	Antipsychotics, Parenteral	\$2,791,177	7.7%	1,468	\$1,901	Y
3	VRAYLAR	Antipsychotics, 2nd Gen	\$1,656,009	4.6%	1,434	\$1,155	Y
4	ABILIFY MAINTENA	Antipsychotics, Parenteral	\$1,518,746	4.2%	782	\$1,942	Y
5	REXULTI	Antipsychotics, 2nd Gen	\$1,451,796	4.0%	1,318	\$1,102	V
6	INVEGA TRINZA	Antipsychotics, Parenteral	\$687,372	1.9%	118	\$5,825	Y
7	BUPROPION XL	Antidepressants	\$575,114	1.6%	26,346	\$22	V
8	TRINTELLIX	Antidepressants	\$566,563	1.6%	1,490	\$380	V
9	SAPHRIS	Antipsychotics, 2nd Gen	\$470,520	1.3%	753	\$625	Y
10	VIIBRYD	Antidepressants	\$467,184	1.3%	1,643	\$284	V
11	FLUOXETINE HCL	Antidepressants	\$460,080	1.3%	33,916	\$14	Y
12	SERTRALINE HCL	Antidepressants	\$454,456	1.3%	45,377	\$10	Y
13	DULOXETINE HCL	Antidepressants	\$445,168	1.2%	30,848	\$14	V
14	TRAZODONE HCL	Antidepressants	\$403,750	1.1%	39,631	\$10	
15	PALIPERIDONE ER	Antipsychotics, 2nd Gen	\$401,535	1.1%	1,825	\$220	V
16	ATOMOXETINE HCL*	ADHD Drugs	\$391,003	1.1%	5,640	\$69	Y
17	ARISTADA	Antipsychotics, Parenteral	\$383,872	1.1%	189	\$2,031	Y
18	Inj, Nusinersen, 0.1mg	Physican Administered Drug	\$348,770	1.0%	2	\$174,385	
19	VENLAFAXINE HCL ER	Antidepressants	\$343,655	0.9%	1,955	\$176	V
20	RISPERDAL CONSTA*	Antipsychotics, Parenteral	\$339,651	0.9%	393	\$864	Y
21	ESCITALOPRAM OXALATE	Antidepressants	\$279,920	0.8%	27,227	\$10	Y
22	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	\$272,151	0.8%	18,841	\$14	
23	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	\$257,039	0.7%	23	\$11,176	Y
24	LAMOTRIGINE	Antiepileptics (oral & rectal)	\$250,351	0.7%	23,782	\$11	Y
25	ARIPIPRAZOLE	Antipsychotics, 2nd Gen	\$229,033	0.6%	14,816	\$15	V
26	BIKTARVY	HIV	\$225,371	0.6%	85	\$2,651	Y
27	CONCERTA*	ADHD Drugs	\$224,616	0.6%	784	\$286	N
28	LAMOTRIGINE ER	Antiepileptics (oral & rectal)	\$224,106	0.6%	2,119	\$106	V
29	AMITRIPTYLINE HCL*	Antidepressants	\$203,282	0.6%	14,485	\$14	Y
30	VENLAFAXINE HCL ER	Antidepressants	\$200,685	0.6%	15,124	\$13	Y
31	LANTUS SOLOSTAR*	Diabetes, Insulins	\$198,215	0.5%	559	\$355	Y
32	QUETIAPINE FUMARATE*	Antipsychotics, 2nd Gen	\$190,412	0.5%	16,320	\$12	Y
33	CITALOPRAM HBR	Antidepressants	\$185,610	0.5%	20,945	\$9	Y
34	EPCLUSA*	Hepatitis C, Direct-Acting Antivirals	\$179,615	0.5%	8	\$22,452	Y
35	Inj., Emicizumab-Kxwh 0.5 Mg	Physican Administered Drug	\$163,821	0.5%	9	\$18,202	
36	FETZIMA	Antidepressants	\$150,187	0.4%	376	\$399	V
37	CHOLBAM*	Bile Therapy	\$149,420	0.4%	2	\$74,710	
38	LAMICTAL	Antiepileptics (oral & rectal)	\$139,988	0.4%	142	\$986	Y
39	CHLORPROMAZINE HCL	Antipsychotics, 1st Gen	\$137,665	0.4%	584	\$236	V
40	BUPROPION HCL SR	Antidepressants	\$134,957	0.4%	9,818	\$14	Y
<b>Top 40 Aggregate:</b>			<b>\$24,035,235</b>		<b>366,128</b>	<b>\$8,097</b>	
<b>All FFS Drugs Totals:</b>			<b>\$36,234,353</b>		<b>625,833</b>	<b>\$596</b>	

# Fixed-cost dose examples

Medication	AAAC (dollars/unit)
Latuda® (lurasidone) 20 mg	40.89137
Latuda® (lurasidone) 40 mg	40.95376
Latuda® (lurasidone) 60 mg	40.93007
Latuda® (lurasidone) 80 mg	40.98689
Latuda® (lurasidone) 120 mg	61.35769

AAAC-Average Actual Acquisition Cost

## Indications and usual dosage:

**Bipolar depression:** Initial 20 mg once daily, increase in 20 mg increments every 2-7 days. Max dose: 120 mg/day

**Schizophrenia:** Initial 40 mg once daily, increase based on response and tolerability. Max dose 160 mg/day

# Fixed-cost dose examples

Medication	AAAC (dollars/unit)
Vraylar® (cariprazine) 1.5 mg cap	39.10998
Vraylar® (cariprazine) 3 mg cap	39.20229
Vraylar® (cariprazine) 4.5 mg cap	39.43612
Vraylar® (cariprazine) 6 mg cap	39.05245

AAAC-Average Actual Acquisition Cost

## Indications and usual dosage:

**Bipolar disorder (*acute manic or mixed*):** Initial: 1.5 mg once daily, may increase to 3 mg on day 2 and in further increments of 1.5 or 3 mg. Range: 3 to 6 mg once daily. Max dose: 6 mg/day

**Bipolar disorder (*bipolar major depression*):** Initial: 1.5 mg once daily, may increase to 3 mg on day 15.

Max dose: 3 mg/day

**Schizophrenia:** Initial: 1.5 mg once daily, may increase to 3 mg on day 2 and in further increments of 1.5 or 3 mg.

Range: 1.5 to 6 mg once daily. Max dose: 6 mg/day

# Fixed-cost dose examples

Medication	AAAC (dollars/unit)
Rexulti® (brexpiprazole) 0.5 mg	37.35972
Rexulti® (brexpiprazole) 1 mg	37.47031
Rexulti® (brexpiprazole) 2 mg	37.26465
Rexulti® (brexpiprazole) 3 mg	37.13953
Rexulti® (brexpiprazole) 4 mg	37.13725

AAAC-Average Actual Acquisition Cost

## Indications and usual dosage:

**Major Depressive disorder:** Initial: 0.5 or 1 mg once daily, may increase weekly to 1 mg (if initial 0.5 mg) or 2 mg (if initial 1 mg). Max dose: 3 mg/day

**Schizophrenia:** Initial: 1 mg once daily, may increase to 2 mg on day 5 and 4 mg on day 8. Max dose: 4 mg/day

# Proposal

- Implement pharmacy edit to consolidate medications with fixed prices across various strengths
- Procedure:
  - Letters to prescribers (already implemented)
  - Point of sale edit
    - Quantity limits (2+ tabs/day) would flag at pharmacy
      - Limit can be set to allow titration
    - Pharmacist would receive message to consolidate dosage
    - Override possible with phone call
    - Prescriber authorization not necessary
    - Does NOT apply to different drug formulations (e.g., Immediate vs extended release)

# Estimated Impact & Cost Saving (net)

➤ Latuda® (lurasidone) → 152 of 1773\* patients

➤ Rexulti® (brexpiprazole) → 21 of 534\* patients

➤ Vraylar® (cariprazine) → 12 of 198\* patients

\$324k/year

# Mental Health Clinical Advisory Group (MHCAG )

## Concerns & Mitigation Strategies

- ***Will/how will the MD receive notification of dosage change?***
  - Retail pharmacists are legally required to notify the prescriber of the change. It would depend on the technology associated with the pharmacy, but most likely this would be via fax until technology advances more to allow for electronic notification.
- ***How will the patient be counselled on the change?***
  - Dispensing pharmacists are required by law to offer counseling, and a patient declining counseling must do so to the pharmacist directly (not another pharmacy staff member, such as a technician). We could include details in our informational fax to pharmacies when starting this program to encourage the need for counseling on changes.
- ***How will we identify appropriate patients or exclude patients during taper, especially cross tapers or slow tapers toward discontinuation?***
  - We can set up the edit to allow 1.75 tablets/day before flagging at the point of sale for consolidation, which should accommodate many tapers. The informational fax to pharmacies will include to call for an override rather than consolidate if patient is actively tapering (up, down, or cross-taper).

# Mental Health Clinical Advisory Group (MHCAG )

## Concerns & Mitigation Strategies

- ***If the medication is being given differently than the manufacturers approved dosage interval (e.g., BID for a Qday drug) will they change it at the pharmacist level to consolidate the dose?***
  - The interval should not change without prescriber authorization. This is a circumstance where the dispensing pharmacist should call for an override to fill the prescription without changes.
- ***If a medication is (intentionally) being given differently than manufacturing labeling (e.g., Latuda 20 mg TID rather than 60 mg Qday) would that prompt a call to the prescriber?***
  - The program itself should not prompt the call, but a dispensing pharmacist would use clinical judgement on calling to question the differing dosing interval from label recommendations.
- ***Retrospective Safety Net Fax:***
  - Patient flagged for this intervention who has a denied claim without a later paid claim (original or a consolidated dose).
  - Automated fax to the pharmacy with that patient's information and the recommended consolidated dose or the phone number for override.
  - Reiteration at pharmacy level that this is not a prescription requiring a PA by the prescriber to process.

## Drug Class Update: Interstitial Lung Disease (formerly Idiopathic Pulmonary Fibrosis)

**Date of Review:** June 2020

**Date of Last Review:** July 2015

**Dates of Literature Search:** 1/1/2015 - 2/1/2020

### **Current Status of PDL Class:**

See **Appendix 1**.

### **Purpose for Class Update:**

Nintedanib (OFEV) received approval from the U.S. Food and Drug Administration (FDA) to treat chronic fibrosing interstitial lung diseases with a progressive phenotype and slow the rate of decline in pulmonary function in patients with interstitial lung disease associated with systemic sclerosis or scleroderma.

### **Research Questions:**

1. What are the differences in efficacy or effectiveness between drugs approved by the FDA to treat idiopathic pulmonary fibrosis (IPF)?
2. What are the differences in adverse events between drugs approved by the FDA to treat IPF?
3. Are there specific populations based on demographic characteristics in which drug treatments for interstitial lung diseases like idiopathic pulmonary fibrosis are associated with greater harm or reduced effectiveness?

### **Conclusions:**

- Four new high-quality systematic reviews and one high-quality clinical practice guideline were identified. Populations studied in patients with IPF were primarily limited to mild-to-moderate disease from the original Phase 3 clinical trials for nintedanib and pirfenidone, but also included several older pharmacological interventions used to manage IPF. Lastly, the new indication for nintedanib was reviewed.
- Few treatments studied in IPF have shown any effect on surrogate outcomes which can be linked through evidence to clinically meaningful outcomes such as mortality.<sup>1</sup>
- There is insufficient evidence to support any intervention for symptom management in IPF.<sup>1</sup>
- There is moderate quality evidence that pirfenidone and nintedanib are effective at improving some measures of lung function (e.g., absolute change in forced vital capacity [FVC]);<sup>1,2</sup> however, quality of evidence is low for more clinically meaningful outcomes (e.g., mortality, acute exacerbations, or dyspnea).<sup>1</sup> Several investigators of the identified systematic reviews expressed caution for broad recommendations for these drugs though one determined there is moderate quality evidence that pirfenidone reduced all-cause mortality, IPF-related mortality and improved progression-free survival.<sup>3</sup> Nintedanib was not evaluated in this systematic review.<sup>3</sup>

- Another systematic review found insufficient evidence to support drugs specific for pulmonary hypertension in IPF patients.<sup>4</sup> Studies have included endothelin receptor antagonists (bosentan, ambrisentan, and macitentan) and sildenafil, a phosphodiesterase type 5 (PDE5) inhibitor. Additionally, there is low quality evidence that adding a PDE5 inhibitor to nintedanib in patients with advanced IPF does not appear to provide significant benefit compared with nintedanib alone.<sup>5</sup>
- The American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and the Latin American Thoracic Society provided an update to their joint 2011 clinical practice guideline in 2015.<sup>6</sup> Strong recommendations were not made for any drug studied for treatment of IPF, although pirfenidone and nintedanib, which are currently the only approved drugs for IPF, received a conditional recommendation for use with moderate confidence in effect estimates.<sup>6</sup> This recommendation placed high value on potential benefit of nintedanib and pirfenidone on patient-important outcomes such as disease progression and lower value on potentially significant adverse effects and the expected cost of treatment.<sup>6</sup> No suggestions for or against combination regimens or sequential therapies were provided except for the recommendation against using prednisone in combination with azathioprine and N-acetylcysteine.<sup>6</sup>
- Nintedanib obtained an expanded indication by the FDA in September 2019 to slow the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease.<sup>7</sup> Nintedanib 150 mg twice daily was studied in a phase 3, 52-week, multi-centered, randomized, double-blind, placebo-controlled trial in 576 patients.<sup>8</sup> For the primary endpoint, the annual rate of change in FVC over a 52-week period was lower in the nintedanib group than in the placebo group (-52.4 mL/year vs. -93.3 mL/year; mean difference [MD], 41.0 mL/year; 95% Confidence Interval [CI], 2.9 to 79.0; p=0.04).<sup>8</sup> No statistically significant differences were found for the key secondary endpoints which included the patient's health-related quality of life (HRQoL), as assessed by the St. George's Respiratory Questionnaire (SGRQ), and their skin thickness, as assessed by the modified Rodnan skin score.<sup>8</sup> No differences in mortality were observed between the nintedanib and placebo groups through the entire trial period.<sup>8</sup> This study provides low quality evidence that nintedanib may slow disease progression with unknown impact on quality of life, skin thickness related to systemic sclerosis, and mortality.
- Nintedanib obtained an expanded indication by the FDA in March 2020 to treat chronic fibrosing interstitial lung diseases with a progressive fibrotic phenotype other than IPF.<sup>7</sup> Nintedanib 150 mg twice daily was studied in a phase 3, 52-week, multi-centered, randomized, double-blind, placebo-controlled trial in 663 patients.<sup>9</sup> The adjusted annual rate of decline in the FVC was -80.8 mL per year in the nintedanib group and -187.8 mL per year in the placebo group (between-group difference, 107.0 mL; 95% CI, 65.4 to 148.5; p<0.001).<sup>9</sup> No statistically significant differences were found for the secondary endpoints which included mortality, acute exacerbations, and overall health status as assessed by the self-administered King's Brief Interstitial Lung Disease questionnaire (K-BILD).<sup>9</sup> This study provides low quality evidence that nintedanib may slow disease progression with unknown impact on mortality and acute exacerbations.
- Warning labeling was updated for both nintedanib and pirfenidone regarding elevated liver enzymes based on case reports and post-marketing studies.<sup>10</sup> Regular monitoring of liver function tests is advised.<sup>10</sup>

#### Recommendations:

- Update clinical prior authorization (PA) criteria (see **Appendix 4**) to approve nintedanib for adults with interstitial lung disease associated with systemic sclerosis or patients with chronic fibrosing interstitial lung disease.
- No change in PDL status of drugs at this time.
- Broaden PDL class to cover drugs with approved indications for interstitial lung diseases, which includes idiopathic pulmonary fibrosis.

## Summary of Prior Reviews and Current Policy

- Nintedanib and pirfenidone were evaluated in patients with mild-to-moderate IPF in placebo-controlled trials and were not compared with each other.<sup>11,12</sup> There is insufficient evidence to determine relative efficacy and safety between the two drugs.
- The placebo-controlled trials did not provide sufficient evidence to determine whether nintedanib had positive effect on mortality, but there was low quality evidence to suggest pirfenidone may decrease mortality in mild-to-moderate IPF patients when data were pooled across studies.<sup>11,12</sup> The data were not statistically significant, but there was a consistent trend toward improved mortality which was associated with slower decline in FVC.<sup>12</sup>
- Phase 3 placebo-controlled trials provided moderate quality evidence that both nintedanib and pirfenidone slow disease progression by reducing decline in FVC.<sup>11,12</sup> Endpoints studied included annual rate of decline in FVC, percent-predicted FVC from baseline and the dichotomous endpoint of absolute FVC decline of 10% or greater.<sup>11,12</sup>
- The nintedanib trials provided low quality evidence that nintedanib may improve quality of life, but the clinical relevance of the results were unclear.<sup>11</sup> The effect of nintedanib on acute exacerbations was inconsistent.<sup>11</sup>
- The pirfenidone trials provided low quality evidence that pirfenidone may slow decline in the 6-minute walk distance test, but the clinical relevance of this result was unclear.<sup>12</sup> Pirfenidone did not appear to improve dyspnea.<sup>12</sup>
- The primary adverse effects from both drugs were diarrhea, nausea, vomiting and abdominal pain.<sup>11,12</sup> Diarrhea was the most common adverse event leading to study discontinuation for nintedanib.<sup>11</sup> Both drugs were also associated with elevated liver enzymes (AST/ALT) which may require dose reduction or interruption in therapy.<sup>11,12</sup> Close monitoring of liver enzymes was advised by the FDA.<sup>11,12</sup>
- Based on this evidence, clinical prior authorization criteria were developed for both drugs that require a diagnosis of IPF; treatment prescribed by a pulmonologist; and an FVC greater than 50%. Concomitant use was prohibited. Renewal of treatment required evidence that IPF had not progressed too rapidly on therapy (defined as a 10% or greater decline in the percent predicted FVC in the previous 12 months).

## Background:

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause occurring in adults predominantly over the age of 50 years.<sup>6,13</sup> The definition of IPF requires the exclusion of other forms of interstitial pneumonia and interstitial lung disease associated with environmental exposure, medication or systemic disease.<sup>14</sup> The prevalence of IPF is estimated between 14 and 27.9 cases per 100,000 persons.<sup>13</sup> Evidence shows that the number of people with IPF is increasing, although the reasons for this are unclear.<sup>1</sup>

IPF is associated with a poor prognosis; median survival is 2 to 3 years after diagnosis.<sup>13</sup> No cure for IPF has been identified. It is unknown if geographic, ethnic, cultural or racial factors play a role in IPF, but several potential risk factors have been identified: 1) environmental factors like smoking history of more than 20 packs per year, exposure to silicon, brass, steel, lead and wood dust, and farming or agricultural work; 2) genetic factors such as familial pulmonary fibrosis, mutations in genes that maintain the length of telomeres, mutations in the surfactant protein C gene and mutations in the mucin 5B promoter region; 3) gastro-esophageal reflux disorder; 4) viral infections, although the role in IPF is not clear; and 5) autoimmunity.<sup>13,14</sup> Diagnosis, evaluation and treatment of IPF requires a multidisciplinary approach, including general practice physicians, pulmonologists, radiologists and pathologists.<sup>13</sup>

The primary symptoms of IPF are unexplained chronic exertional dyspnea and a cough, which can have a considerable impact on day-to-day life.<sup>1,14</sup> IPF was once thought to progress at a steady, predictable rate, but it is now known that this is often not the case.<sup>1</sup> Many people with IPF deteriorate rapidly, while others may have periods of relative stability.<sup>1</sup> IPF is a difficult condition to manage, particularly in the later stages.<sup>1</sup>

Treatments aim to reduce symptoms and improve survival.<sup>1</sup> N-acetylcysteine (NAC) combined with prednisone and azathioprine was the treatment-of-choice for several years until a study found the triple therapy combination resulted in higher mortality and hospital admissions compared to placebo or NAC alone.<sup>15</sup> Two antifibrotic agents, nintedanib and pirfenidone, are the only two drugs with confirmed efficacy in slowing functional decline and disease progression in IPF patients. Both drugs received approval from the FDA in 2014 for the treatment of IPF. Although pirfenidone and nintedanib have both demonstrated efficacy in reducing rates of disease progression compared with placebo, these drugs do not cure IPF and patients continue to experience lung function decline while on treatment.<sup>16-18</sup> The long-term safety and tolerability of nintedanib and pirfenidone have been evaluated in open-label follow-up studies.<sup>19,20</sup> The safety profiles for both drugs included gastrointestinal adverse events, which are consistent with the known safety profile of the drugs from the phase 3 trials<sup>16-18</sup>, and no new safety signals were observed.<sup>19,20</sup> Combined treatment with pirfenidone and nintedanib has been studied for safety and tolerability, but efficacy has not been established.<sup>21,22</sup> The frequency of common treatment-emergent adverse effects seen with either drug alone is higher when the two are combined, with mild to moderate nausea, vomiting and diarrhea being the most common.<sup>21,22</sup>

Non-pharmacologic treatment also plays a vital role in the management of patients with IPF.<sup>13</sup> Pulmonary rehabilitation in early stages of IPF has shown short-term improvement in walking distance, symptoms and quality of life.<sup>13</sup> Patients with resting hypoxemia should use long-term oxygen therapy based on chronic obstructive pulmonary disease and chronic respiratory failure studies.<sup>13</sup> Ultimately, lung transplantation is the most effective and reliable treatment for patients with IPF.<sup>13</sup> Lung transplantation 5-year survival ranges from 50-56% and 10-year survival rate is 30%.<sup>13</sup>

Clinically meaningful outcomes for IPF include mortality, morbidity [e.g., acute exacerbations or disease progression evaluated with surrogate endpoints of FVC or carbon monoxide diffusing capacity (DLCO)], symptom relief (e.g., dyspnea), functioning [e.g., 6-minute walking distance (6MWD) test], and quality of life. Validated instruments to assess clinically meaningful subjective outcomes and their minimum clinically important difference (MCID) are not clearly defined for IPF. An exception might be the SGRQ, a 50-item patient-administered questionnaire that assesses HRQoL in patients with respiratory disease.<sup>23</sup> The questionnaire is comprised of 3 domains: impact, symptoms and activity.<sup>23</sup> The symptoms domain addresses the frequency and severity of respiratory symptoms; the activity domain assesses activities that cause or are limited by breathlessness and the impact domain assesses a range of aspects around social functioning and the psychological impact of the disease.<sup>23</sup> Domain and total scores range from 0 to 100, with higher scores indicating worse HRQoL.<sup>23</sup> The suggested MCID for patients with IPF is a change of 4-5 points but this has not been validated in other interstitial lung diseases.<sup>23</sup>

Composite scoring systems have been developed utilizing physiological (e.g., FVC or DLCO) and radiographic variables in an attempt to provide more accurate prognostic information. However, this composite approach has not been tested in any prospective clinical trials to date and its clinical utility is unknown.<sup>14</sup> Although the 6MWD test is widely used in clinical practice, its prognostic value is limited due to lack of procedural standardization in patients with IPF. Some studies have suggested that desaturation (i.e., a decline in oxygen saturation to below 88%) during the 6MWD test is a marker for increased risk of mortality. Shorter walk distance and delayed heart-rate recovery after walk testing have been associated with an increased risk of subsequent mortality. However, it is unclear if desaturation, distance walked, and other variables measured during 6MWD test in this population are reproducible.<sup>14</sup>

Acute exacerbations are an especially relevant outcome that can be studied in clinic trials since 50% of patients admitted for an acute IPF exacerbation die during hospitalization.<sup>13</sup> Acute exacerbations are treated with high-dose corticosteroid therapy and broad-spectrum antibiotics despite the lack of conclusive evidence demonstrating their benefit.<sup>13</sup>

Utilization of pirfenidone and nintedanib is infrequent in the fee-for-service (FFS) population, with typically no more than one or two patients with claims each quarter.

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**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:**The Clinical Efficacy of Pulmonary Hypertension-Specific Agents in IPF (2020)<sup>4</sup>:

Pulmonary hypertension (PH) is common in patients with IPF and is associated with poor outcomes.<sup>4</sup> A systematic review with meta-analysis was performed to determine the clinical efficacy of PH-specific therapeutic agents for IPF patients.<sup>4</sup> The investigators used the following inclusion criteria: 1) published studies in peer-reviewed journals; 2) RCTs that compared pulmonary hypertension-specific agents with controls; 3) active interventions for one of the four PH-specific agent classes: endothelin receptor antagonists (ERAs), prostacyclin analogues, soluble guanylate cyclase stimulators, or PDE5 inhibitors; 4) patients diagnosed with IPF according to international guidelines; and 5) clinical outcomes and adverse events data available.<sup>4</sup> The primary outcome studied was all-cause mortality.<sup>4</sup> Risk of bias was assessed using the following criteria: sequence generation/ allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other sources of bias.<sup>4</sup> Risk of bias was labeled as high, low, or unclear. A total of 43 eligible articles were selected, and of these, 10 studies reported at least one primary (all-cause mortality) or secondary outcome (lung function, quality of life, functioning, adverse events) that could be combined into a meta-analysis.<sup>4</sup> The number of patients in the trials ranged from 24 to 616. The active interventions were ERAs in 6 trials (bosentan in 4; ambrisentan in one; macitentan in one) and a PDE5 inhibitor in 4 trials (sildenafil in all).<sup>4</sup> One study included idiopathic nonspecific interstitial pneumonia as well as IPF, and another study included results from a combined therapy of nintedanib and sildenafil.<sup>4</sup> One trial was judged to be high risk of bias because it was non-blinded to participants, researchers and outcome assessment.<sup>4</sup>

Data regarding the effects of PH-specific agents on all-cause mortality in IPF patients were available in 8 trials.<sup>4</sup> All-cause mortality did not differ between the PH-specific agent group and the control group (placebo or no treatment) [hazard ratio (HR) 0.99; 95% CI, 0.92 to 1.06; p=0.71; moderate heterogeneity:  $I^2=30\%$ ; p=0.19].<sup>4</sup> Even after excluding one outlier study based on sensitivity analysis, all-cause mortality did not differ between the groups, although the heterogeneity decreased (HR 0.99; 95% CI, 0.92 to 1.06; p=0.78;  $I^2=0\%$ ).<sup>4</sup> Because the result for the primary outcome was not statistically significant, a subgroup analysis planned *a priori* was performed. When the analysis was restricted to patients treated with ERAs or PDE5 inhibitors, all-cause mortality did not differ between the groups (HR 1.09; 95% CI, 0.63 to 1.86; p=0.77;  $I^2=56\%$  for ERAs and HR 0.98; 95% CI, 0.92 to 1.06; p=0.67;  $I^2=0\%$  for the PDE5 inhibitor sildenafil).<sup>4</sup> All-cause mortality also did not differ based on sample size ( $\geq 200$  vs.  $< 200$ ), age ( $\geq 65$  y vs.  $< 65$  y), mean FVC ( $\geq 60\%$  vs.  $< 60\%$ ), or mean DLCO ( $\geq 30\%$  vs.  $< 30\%$ ).<sup>4</sup>

Seven trials reported data on changes in FVC and DLCO from baseline.<sup>4</sup> Change in FVC did not differ between the PH-specific agent group and the control group (MD 0.69% predicted; 95% CI, -0.36 to 1.74%; p=0.20; I<sup>2</sup> =0% for FVC % predicted, and MD 0.06 L; 95% CI -0.11 to 0.25 L; p=0.48; I<sup>2</sup> =0% for FVC L).<sup>4</sup> The decline in patient-predicted DLCO also did not differ in the PH-specific agent group and the control group (MD 0.81%; 95% CI, -0.24 to 1.87; p=0.13; I<sup>2</sup> =0%).<sup>4</sup> Mean change in DLCO also did not differ.<sup>4</sup> Three trials reported quality of life for IPF patients as measured by the St. George Respiratory Questionnaire (SGRQ) total score, a disease-specific instrument used in IPF.<sup>4</sup> Pooled estimates showed a statistically significant improvement in the SGRQ total score in the PH-treatment group compared to controls (MD -3.16 points; 95% CI, -5.34 to -0.97 points; p=0.005; I<sup>2</sup> =0%).<sup>4</sup> However, no differences between the 2 groups were found from 2 trials that reported the Borg dyspnea index score after walk test (MD 0.23 points; 95% CI, -1.21 to 1.68 points; p=0.75; I<sup>2</sup> =69%) or from 3 trials that reported change in the 6-minute walk distance test (MD -2.16 m; 95% CI, -8.00 to 3.68 m; p=0.47; I<sup>2</sup> =22%).<sup>4</sup> Serious adverse events were also similar between the study and control groups (RR 0.97; 95% CI, 0.82 to 1.15; p=0.74; I<sup>2</sup> =17%).<sup>4</sup>

The investigators concluded that this systematic review provides insufficient evidence to support PH-specific agents in IPF patients.<sup>4</sup>

#### The Clinical Effectiveness and Cost-effectiveness of Treatments for IPF (2015)<sup>1</sup>:

The Health Technology Assessment program, part of the National Institute for Health Research, produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the U.K. National Health Service (NHS).<sup>1</sup> The objective of this report was to evaluate the clinical effectiveness and cost-effectiveness of the different treatment strategies used within the NHS for IPF through systematic reviews of the evidence.<sup>1</sup> The report was funded by the National Institute for Health Research.<sup>1</sup> For the systematic review of clinical effectiveness, studies were eligible for inclusion if the patients had a confirmed diagnosis of IPF and the interventions under study were currently used to manage symptoms or modify IPF.<sup>1</sup> Randomized clinical trials were eligible for inclusion.<sup>1</sup> Where appropriate, the studies were combined in a meta-analysis and heterogeneity was assessed.<sup>1</sup> A network meta-analysis (NMA) focusing on pharmacological treatments for IPF which assessed FVC end points was undertaken on 10 studies.<sup>1</sup> The FVC end point was measured on two continuous scales, and the NMA used the standardized mean difference approach.<sup>1</sup> Systematic literature searches were undertaken to identify full economic evaluations of interventions to manage IPF, and to assess the HRQoL for people with IPF.<sup>1</sup> Studies reporting HRQoL in people with IPF were eligible for inclusion if they used either generic preference-based measures or the SGRQ.<sup>1</sup> Cost-effectiveness results from this report will not be discussed because the economic modelling is relevant to the UK setting.

Eight hundred and fourteen references were identified by searches for clinical effectiveness.<sup>1</sup> Ten studies of patients with mild to moderate IPF were included, of which 1 evaluated azathioprine, 3 evaluated NAC (alone or in combination), 4 evaluated pirfenidone, 1 evaluated nintedanib, and 1 evaluated sildenafil.<sup>1</sup> Study quality was generally good with a low risk of bias.<sup>1</sup>

In a small RCT, treatment with azathioprine and prednisolone led to an improvement in survival compared with placebo and prednisolone when an age-adjusted analysis was used (HR 0.26; 95% CI, 0.08 to 0.88), suggesting a 64% reduction in the risk of death with azathioprine.<sup>1</sup> The likely inclusion of participants with non-specific interstitial pneumonia may explain this treatment effect, and the small sample size and potential risk of bias in this study should be considered when interpreting these data.<sup>1</sup> There was no effect on lung function (MD in % predicted FVC at 12 months: 4.8%; p=0.87; MD in % predicted DLCO at 12 months: 6.4%; p=0.70).<sup>1</sup> Follow-up was 12 months.<sup>1</sup>

Nintedanib 300 mg daily was more favorable than placebo on some measures of lung function (absolute change in FVC from baseline for nintedanib -0.06 L [95% CI, -0.13 to 0.01] vs. placebo -0.23 L [95% CI, -0.30 to -0.16]; MD 0.17 L; p=0.001; absolute change in % predicted FVC for nintedanib -1.04% [95% CI, -2.98% to

0.91%] vs. placebo -6.00% [95% CI, -8.01 to -4.00%]; MD 4.96%;  $p < 0.001$ ), rates of acute exacerbations (nintedanib 2.4 per 1000 patient years vs. placebo 15.7 per 1000 patient years [RR 0.16; 95% CI, 0.03 to 0.70;  $p = 0.02$ ]) and the number of all-cause deaths (nintedanib 7 vs. placebo 9); however, the primary outcome of annual rate of decline in FVC was not statistically significantly different between groups in a 54-month study (nintedanib -0.06 L [95% CI, -0.14 to 0.02 L] vs. placebo -0.19 L [95% CI, -0.26 to -0.12 L]; MD 0.13 L;  $p = 0.06$ ).<sup>1</sup>

Treatment with NAC was evaluated in 3 studies. In 2 studies, NAC 600 mg was administered orally three times daily in combination with azathioprine and prednisolone; NAC was studied as a single agent at 352.4 mg diluted with saline to a total volume of 4 mL and nebulized twice daily in the third study.<sup>1</sup> Follow-up was approximately 12 months in these studies.<sup>1</sup> Study results were mixed, with no benefit from triple therapy on change in FVC compared with placebo in one study (-0.24 L vs. -0.23 L, respectively [MD -0.01 L; 95% CI, -0.14 to 0.11;  $p = 0.85$ ]); however, there was a benefit on FVC when triple therapy was compared with double therapy (placebo, azathioprine plus prednisolone) in another study (2.27 L vs. 2.10 L, respectively [MD 0.18 L; 95% CI, 0.03 to 0.32;  $p = 0.02$ ]).<sup>1</sup> Inhaled single-therapy NAC did not have a statistically significant effect compared with a control.<sup>1</sup> Secondary outcomes (e.g., HRQoL, 6MWD and DLCO) were reported, similarly with mixed results across the 3 studies.<sup>1</sup> The 2 studies with triple-therapy interventions had a low risk of bias; however, the study using nebulized NAC had an unclear risk of bias.<sup>1</sup>

Pirfenidone was studied in 4 RCTs, and meta-analysis of FVC shows that pirfenidone appears to demonstrate an effect when compared with placebo treatment (MD 0.24 L; 95% CI, 0.06 to 0.41;  $p = 0.008$ ;  $I^2$  45%).<sup>1</sup> However, caution is required in interpreting these data as the outcomes pooled were different, and as a consequence a standardized mean difference analysis was undertaken; in addition, the timing of assessment of these outcomes varied (from 48 weeks to 72 weeks).<sup>1</sup> A random-effects meta-analysis demonstrated a favorable effect of pirfenidone on the proportion of patients with a decline in FVC of 10% or more (RR 0.62; 95% CI, 0.41 to 0.93;  $p = 0.02$ ;  $I^2$  57%).<sup>1</sup> Results for secondary outcomes were generally seen to be less favorable to pirfenidone. Differences in mean change from baseline in the percent predicted DLCO at 72 weeks was not statistically different between pirfenidone and placebo (MD 0.68; 95% CI, -0.87 to 3.22;  $p = 0.6$ ).<sup>1</sup> In addition, no differences were found between pirfenidone and placebo in the 6MWD.<sup>1</sup> The rate of acute exacerbations was studied in 2 trials but results were mixed, favoring pirfenidone over placebo in one trial and placebo over pirfenidone in the other trial.<sup>1</sup> Health-related quality of life outcomes were not reported.

One study assessed sildenafil for those with moderate to severe IPF; the patients in this study also had evidence of pulmonary hypertension.<sup>1</sup> Results on the primary outcome, a 20% improvement on the 6MWD test, were not statistically significant between the sildenafil and placebo groups (10% vs. 7%, respectively;  $p = 0.39$ ).<sup>1</sup> Results for secondary outcomes were mixed, with some favoring sildenafil (quality of life and DLCO) and others favoring placebo (incidence of acute exacerbations and FVC).<sup>1</sup> This study followed participants for 12 weeks and had an unclear risk of bias.<sup>1</sup>

Adverse events from the pharmacological interventions were generally mild to moderate and were reasonably well balanced between the treatment and placebo arms across the studies.<sup>1</sup> Severe adverse events appeared to be more common in one study in those treated with triple therapy.<sup>1</sup>

The fixed-effects NMA found only nintedanib and pirfenidone to have a statistically significant improvement in FVC over placebo.<sup>1</sup> A head-to-head comparison of nintedanib versus pirfenidone showed a trend favoring nintedanib, but this was not statistically significant.<sup>1</sup> Caution is required in the interpretation of the results of the NMA.

The investigators concluded that the current evidence suggests that there are few treatments that have any effect on surrogate outcomes which can be linked through evidence to patient-related outcomes such as mortality.<sup>1</sup> There is overall a scarcity of studies on interventions in symptom management. Pirfenidone

and nintedanib appear to be clinically effective; however, general recommendations cannot be made in terms of their cost-effectiveness owing to limitations in the evidence base.<sup>1</sup> Limitations to this report include there being few direct comparisons of treatments identified.<sup>1</sup> An indirect comparison through an NMA was performed; however, caution is recommended in the interpretation of these results.

#### The Effectiveness and Safety of Pirfenidone, Nintedanib and N-acetylcysteine for the Treatment of Idiopathic Pulmonary Fibrosis (2016)<sup>2</sup>:

A systematic review of the effectiveness and safety of pirfenidone, nintedanib and NAC for treatment of IPF versus placebo was performed.<sup>2</sup> Lack of head-to-head RCTs of treatment interventions drove the decision to systematically review placebo-controlled high-quality RCTs of at least 6 months' duration.<sup>2</sup> Patients enrolled in the study were suffering from IPF diagnosed by high-resolution computed tomography or biopsy.<sup>2</sup> Data from included studies were extracted and checked for study characteristics and duration, doses of medications, disease characteristics, age, gender, smoking habits, smoking history, FVC, DLCO, 6MWD, time since diagnosis, weight and Jadad score.<sup>2</sup> The Jadad score was used to assess the quality of the studies, and a score of 3 or more was required to be included in the meta-analysis.<sup>24</sup> The risk of publication bias was assessed by applying the funnel plot and Egger's test.<sup>2</sup> Significant moderate to high levels of heterogeneity were considered for  $I^2$  greater than 50%.<sup>2</sup> Results were obtained from 3847 IPF patients from 12 RCTs.<sup>2</sup> Funnel plot analysis did not find publication bias for the analysis of the impact of pirfenidone, nintedanib and NAC on all the investigated outcomes.<sup>2</sup> Of note, in conflict of interest disclosure, nearly all of the authors of this systematic review had financial associations with Boehringer Ingelheim Pharmaceuticals, the manufacturer of nintedanib.<sup>2</sup>

The meta-analysis of these trials found that both pirfenidone or nintedanib, but not NAC, improved the standardized mean difference (SMD) of change from baseline in FVC (pirfenidone 0.26 L; 95% CI, 0.15 to 0.37;  $I^2$  29%; nintedanib 0.37 L; 95% CI, 0.26 to 0.48;  $I^2$  16%; NAC 0.1 L; 95% CI, -0.11 to 0.30;  $I^2$  10%) versus placebo. The risk difference (RD) for FVC decline of 10% or more favored pirfenidone and nintedanib, but not NAC (pirfenidone RD -0.10%; 95% CI, -0.14 to -0.06;  $I^2$  4%; nintedanib RD -0.12%; 95% CI, -0.21 to -0.03;  $I^2$  66%; NAC RD -0.06%; 95% CI, -0.20 to 0.08;  $I^2$  63%), versus placebo.<sup>2</sup> Nintedanib, but not pirfenidone nor NAC reduced acute exacerbations (nintedanib RD -0.05%; 95% CI, -0.10 to -0.01;  $I^2$  59%; pirfenidone RD -0.01%; 95% CI, -0.05 to 0.03;  $I^2$  51%; NAC RD 0.03%; 95% CI, -0.04 to 0.09;  $I^2$  70%) compared with placebo.<sup>2</sup> Data on the 6MWD variable were not suitable for performing an unbiased meta-analysis.<sup>2</sup>

Pirfenidone and nintedanib did not increase the RD of serious adverse events (SAE) (pirfenidone 0.00; 95% CI, -0.02 to 0.02;  $I^2$  0%; nintedanib -0.02; 95% CI -0.06 to 0.03;  $I^2$  0%) versus placebo, while NAC slightly increased risk for SAE but was not statistically significant (RD 0.12; 95% CI, -0.05 to 0.29;  $I^2$  80%).<sup>2</sup> Nintedanib, but not pirfenidone nor NAC, protected against both overall and respiratory-specific risk of death (nintedanib -0.03; 95% CI, -0.06 to -0.001;  $I^2$  28%; pirfenidone -0.01; 95% CI, -0.02 to 0.00;  $I^2$  24%; NAC 0.03; 95% CI, -0.02 to 0.08;  $I^2$  18%) compared with placebo.<sup>2</sup> The most common adverse events associated with the administration of FDA-approved doses of pirfenidone were rash (30.34%), nausea (25.68%), cough (19.42%), dizziness (17.98%), headache (16.05%), anorexia (13.00%), dyspepsia (12.68%), dyspnea (11.08%) and insomnia (10.43%), whereas those associated with approved doses of nintedanib were diarrhea (60.68%), nausea (24.34%), cough (12.86%), nasopharyngitis (12.86%), vomiting (11.62%) and decreased appetite (11.07%).<sup>2</sup> However, overall 40% of very common (i.e.,  $\geq 10\%$ ) and 87% of common (i.e.,  $\geq 1\%$  to 10%) adverse events were also observed with similar frequency in the placebo arms.<sup>2</sup>

Overall, approved doses of pirfenidone and nintedanib, but not NAC, reduced progression of IPF in terms of improved SMD change from baseline in FVC and the RD of FVC decline compared with placebo, but with a safety profile similar to that of placebo.<sup>2</sup>

#### The Effectiveness and Safety of Pirfenidone for Idiopathic Pulmonary Fibrosis (2015)<sup>3</sup>:

The aim of another systematic review and meta-analysis was to assess the efficacy and safety of pirfenidone on several physiological and clinical outcomes in IPF (including mortality, acute exacerbations and worsening of IPF).<sup>3</sup> Studies were eligible for inclusion if they limited their investigation to adults age 18 years or older with IPF, were RCTs that compared pirfenidone with placebo, and studied at least one clinical outcome.<sup>3</sup> The included outcomes in the analysis were: 1)

change in all-cause mortality; 2) change in IPF-related mortality; 3) progression-free survival (PFS); 4) decrease in predicted FVC; 5) worsening of idiopathic pulmonary fibrosis; 6) acute exacerbation; 7) change in 6MWD test; 8) and adverse effects.<sup>3</sup>

A total of 557 studies were identified, but only 5 RCTs included in 4 publications met inclusion criteria and were analyzed.<sup>3</sup> **Table 1** summarizes the findings following the GRADE approach. Absolute values were not reported for each of the outcomes.

**Table 1.** Summary of findings from Studies of Pirfenidone for IPF.<sup>3</sup>

Outcome	Relative Effect (95% CI)	Participants	Quality of Evidence (GRADE)
All-cause mortality	RR 0.53 (0.32 to 0.88)	N=1247 (3 RCTs)	Moderate
Progression-free Survival	RR 0.82 (0.73 to 0.92)	N=728 (3 RCTs)	Moderate
Acute Exacerbation	RR 0.59 (0.19 to 1.84)	N=235 (2 RCTs)	Low
Worsening of IPF	RR 0.64 (0.50 to 0.83)	N=1615 (5 RCTs)	Moderate
Change in 6MWD	RR 0.74 (0.64 to 0.86)	N=1236 (3 RCTs)	High
Change in aminotransferases	RR 2.26 (1.33 to 3.83)	N=764 (5 RCTs)	Moderate

Abbreviations: CI = confidence interval; RCT = randomized clinical trial; RR = risk ratio; 6MWD = 6-minute Walk Distance test.

Three RCTs (1247 patients) were identified that reported the effect of pirfenidone and mortality.<sup>3</sup> The meta-analysis included 623 patients in the intervention group and 624 in the placebo group.<sup>3</sup> Pirfenidone decreased all-cause mortality and IPF-related mortality at week 52 relative to placebo (see Table 1).<sup>3</sup> Quality of evidence was downgraded to moderate because of indirectness of this outcome.<sup>3</sup>

Five RCTs were identified that reported the effect of pirfenidone and PFS.<sup>3</sup> Pooled data from all studies were evaluated at week 52.<sup>3</sup> When PFS was not reported at week 52, data were extracted to 52 weeks from Kaplan-Meier curves.<sup>3</sup> The meta-analysis included 850 patients in the pirfenidone group and 863 in the placebo group.<sup>3</sup> Pirfenidone decreased PFS at week 52 compared with placebo (see Table 1).<sup>3</sup> Quality of evidence was downgraded to moderate because of indirectness.<sup>3</sup>

Four RCTs reported acute exacerbation of IPF.<sup>3</sup> The meta-analysis included 235 patients in the pirfenidone group and 139 in the placebo group.<sup>3</sup> Pirfenidone did not improve acute exacerbations of IPF compared with placebo (see Table 1).<sup>3</sup> Quality of evidence was downgraded to low because of indirectness and imprecision between results.<sup>3</sup>

Three RCTs reported worsening of IPF as a secondary endpoint, a composite outcome that included acute IPF exacerbations, IPF-related death, lung transplantation or respiratory hospitalization.<sup>3</sup> The meta-analysis included 786 patients in the pirfenidone group and 728 in the placebo group.<sup>3</sup> Pirfenidone improved worsening of IPF compared with placebo (see Table 1).<sup>3</sup> Quality of evidence was downgraded to moderate because of indirectness.<sup>3</sup>

Five RCTs reported the effect of pirfenidone on FVC or vital capacity (VC).<sup>3</sup> In 3 RCTs, change in percentage of predicted FVC greater than 10% were reported.<sup>3</sup> The meta-analysis included 623 patients in the pirfenidone group and 624 patients in the placebo group.<sup>3</sup> Pirfenidone decreased the risk of greater than 10% change in FVC compared with placebo (see Table 1).<sup>3</sup> Quality of evidence was downgraded to moderate due to imprecision.<sup>3</sup>

Three RCTs reported the effect of pirfenidone on change in 6MWD.<sup>3</sup> The meta-analysis included 617 patients in the pirfenidone group and 619 patients in the placebo group.<sup>3</sup> Pirfenidone improved 6MWD compared with placebo (see Table 1).<sup>3</sup> The quality of evidence was rated as high.<sup>3</sup>

Five RCTs were identified that reported the effect of pirfenidone and adverse effects.<sup>3</sup> Pooled data from all studies were evaluated at the end of each trial.<sup>3</sup> The meta-analysis included 857 patients in the pirfenidone group and 766 in the placebo group.<sup>3</sup> Pirfenidone was not associated with severe adverse events (RR 1.02; 95% CI, 0.93 to 1.11; I<sup>2</sup> 2%) compared with placebo.<sup>3</sup> However, other adverse events such as photosensitivity (RR 4.92; 95% CI, 2.10 to 11.53; I<sup>2</sup> 57%) or change in aminotransferases (RR 2.26; 95% CI, 1.33 to 3.83; I<sup>2</sup> 23%) were more frequent with pirfenidone compared with placebo.<sup>3</sup> The quality of evidence was graded as moderate because of imprecision.<sup>3</sup>

The investigators found pirfenidone results in statistically significant differences in physiologic and clinically meaningful outcomes such as reduction in all-cause mortality, IPF-related mortality, worsening and exacerbation of IPF and PFS.<sup>3</sup> As a result, they concluded that pirfenidone use should be considered not only for its benefit in pulmonary function tests but also for its impact on clinically meaningful outcomes.<sup>3</sup>

After further review, 5 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).<sup>25-29</sup>

#### **New Guidelines:**

The American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and the Latin American Thoracic Society (ALAT) (2015)<sup>6</sup>:

This update of the 2011 guideline<sup>14</sup> was developed by a multidisciplinary committee of pulmonologists with recognized IPF expertise, general pulmonologists, a pulmonologist-methodologist, and allergist-methodologist, a general internist, a chest radiologist, a pulmonary pathologist, an information scientist, and a patient with IPF.<sup>6</sup> The committee worked with 5 health research methodologists who had expertise in evidence synthesis and the guideline development process. The Committee conducted systematic reviews and prepared the systematic evidence summaries following the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.<sup>6</sup>

Committee members signed a confidentiality agreement and disclosed all potential conflicts of interest.<sup>6</sup> All of the 8 pulmonologists with recognized IPF expertise were considered to either have major financial or intellectual conflicts based on disclosures or participation in IPF clinical studies.<sup>6</sup> Although they were permitted to participate in the discussions of the evidence with the rest of the committee, they were instructed to abstain from discussions related to the evidence to decision framework, formulating and grading recommendations, and voting on recommendations.<sup>6</sup> Adherence to the rules was strict, with one of the committee co-chairs responsible for monitoring the discussions for adherence to these rules.<sup>6</sup> The remaining 9 nonconflicted committee members were allowed unrestricted participation.<sup>6</sup>

This guideline does not provide recommendations for one treatment regimen over another. With the exception of the recommendation against using prednisone with azathioprine and N-acetylcysteine, the guideline does not provide suggestions for or against combination regimens or sequential therapies.<sup>6</sup> The committee suggested each recommendation be weighed individually (i.e., 2 recommendations with the same strong or conditional rating should not be considered equivalent recommendations), factoring in all components used to determine the grade of the recommendation, including the confidence in effect estimates, outcomes studied, desirable and undesirable consequences of treatment, cost of treatment, and feasibility of treatment.<sup>6</sup>

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The committee selected outcomes of interest for each research question.<sup>6</sup> All outcomes were identified *a priori*, and the committee explicitly rated their relative importance from the perspective of a patient with IPF.<sup>6</sup> Ranking outcomes by their relative importance helped focus attention on clinically meaningful outcomes most relevant to patients and helped to resolve or clarify potential disagreements in decision making.<sup>6</sup> Examples of clinically meaningful outcomes were mortality or disease progression.<sup>6</sup> Disease progression can be measured using multiple outcome measures, and was defined by the committee as increasing respiratory symptoms, worsening pulmonary function test (PFT) results, progressive fibrosis on high-resolution computed tomography scan, acute respiratory decline, or death.<sup>6</sup> Changes over time in FVC or DLCO were considered indirect measures of disease progression.<sup>6</sup>

Data from identified studies with the same treatment were pooled and meta-analyses were reviewed.<sup>6</sup> Overall confidence in effect estimates for each outcome was assessed following the GRADE approach, based on the following criteria: risk of bias, precision, consistency, directness of the evidence, risk for publication bias, presence of dose-effect relationship, magnitude of effect, and assessment of the effect of plausible residual confounding or bias.<sup>6</sup> Each of the following factors was considered in development of each recommendation: the quality of the evidence, the balance of desirable and undesirable consequences of compared management options, the assumptions about the values and preferences associated with the decision, the implications for resource use and health equity, the acceptability of intervention to stakeholders, and the feasibility of implementation.<sup>6</sup>

The recommendations were graded as “strong” or “conditional”, according to the GRADE approach.<sup>6</sup> Conditional recommendations are synonymous with weak recommendations.<sup>6</sup> Conditional recommendations require clinicians to recognize that different treatment choices will be appropriate for individual patients based on their values and preferences.<sup>6</sup>

#### Recommendations:

1. The recommendation **against** the use of the following agents for the treatment of IPF is **strong**:
  - a. Anticoagulation (warfarin) (low confidence in effect estimates).<sup>6</sup>
    - i. This recommendation is based on lack of benefit (no change in FVC) and increased mortality (RR 4.73; 95% CI, 1.42 to 15.77) with warfarin (goal INR 2.0 – 3.0) versus placebo in patient with IPF.<sup>6</sup>
  - b. Imatinib, a selective tyrosine kinase inhibitor against platelet-derived growth factor (PDGF) receptors (moderate confidence in effect estimates).<sup>6</sup>
    - i. This recommendation is based on lack of efficacy and high cost of treatment. No differences in mortality or progression of IPF were found between imatinib and placebo in patients with IPF. Imatinib is associated with higher rates of adverse events than placebo in this population.
  - c. Combination prednisone, azathioprine, and N-acetylcysteine (low confidence in effect estimates).<sup>6</sup>
    - i. Immune suppression was considered an important part of IPF treatment, but studies have shown higher rates of mortality and hospitalization in IPF patients treated with the combination of prednisone, azathioprine and N-acetylcysteine versus placebo. In addition, no differences in FVC change or quality-of-life indices were found with this drug combination.<sup>6</sup>
  - d. Selective endothelin receptor antagonist (ambrisentan) (low confidence in effect estimates).<sup>6</sup>
    - i. A 52-week placebo-controlled RCT was stopped early for lack of benefit and high likelihood of harm with ambrisentan in IPF patients (HR 2.08; 95% CI, 0.75 to 5.76; low confidence). Patients who received ambrisentan also experience increased disease progression regardless of presence or absence of pulmonary hypertension.<sup>6</sup>
2. The recommendations **for** the use of the following agents for the treatment of IPF are **conditional**:

- a. Nintedanib, a tyrosine kinase inhibitor that targets multiple tyrosine kinases, including vascular endothelial growth factor, fibroblast growth factor, and PDGF receptors (moderate confidence in effect estimates).<sup>6</sup>
  - i. Nintedanib was evaluated in 3 RCTs in patients with mild to moderate IPF. The first RCT was a phase 2 trial that did not find statistically significant differences in mortality between placebo and nintedanib 50 mg daily, 100 mg daily, 150 mg daily and 150 mg twice daily. The percentage of patients with more than 10% FVC decline at 12-month follow-up was lower with 150 mg twice daily versus placebo ( $p=0.004$ ), but no difference was found between placebo and the other doses. However, fewer patients experienced IPF exacerbations with any dose of nintedanib compared to placebo (HR 0.16; 95% CI, 0.04 to 0.70). The other 2 identical phase 3 trials compared nintedanib 150 mg twice daily to placebo for 52 weeks and found no difference in mortality (RR 0.70; 95% CI, 0.44 to 1.11) or acute exacerbations of IPF (HR 0.64; 95% CI, 0.39 to 1.05); however, fewer patients treated with nintedanib had a more than 10% absolute decline in FVC (RR 1.16; 95% CI, 1.06 to 1.27) and annual rate of change in FVC was slower with nintedanib (MD 125.2 mL; 95% CI, 77.7 to 172.8 mL). More patients treated with nintedanib reported an adverse event (RR 1.07; 95% CI, 1.03 to 1.11) with diarrhea being the most prevalent.<sup>6</sup>
  - ii. This recommendation places high value on potential benefit of nintedanib on patient-important outcomes such as disease progression and lower value on potentially significant adverse effects and the expected cost of treatment.<sup>6</sup>
  - iii. The available evidence focuses on patients with IPF with mild to moderate impairment in PFTs, and it is unknown whether the therapeutic benefits would differ in patients with a more severe impairment.<sup>6</sup>
  - iv. The evidence does not suggest an optimal duration of therapy, and it is unknown if there is loss in treatment effect with ongoing therapy.<sup>6</sup>
- b. Pirfenidone, an oral antifibrotic drug shown to regulate profibrotic and proinflammatory cytokine cascades in vitro and reduce fibroblast proliferation and collagen synthesis in animal models of lung fibrosis (moderate confidence in effect estimates).<sup>6</sup>
  - i. Pooled analyses of clinical trials suggest possible, but not statistically significant, improvement in mortality (RR 0.70; 95% CI, 0.47 to 1.02; moderate confidence), reduced rate of FVC decline (SMD, 0.23; 95% 0.06 to 0.41; high confidence), and increased rate of photosensitivity (high confidence), fatigue (moderate confidence), stomach discomfort (moderate confidence) and anorexia (high confidence) in patients treated with pirfenidone.<sup>6</sup>
  - ii. This recommendation places high value on patient-important outcomes such as disease progression as measured by rate of FVC decline and mortality and a lower value on potentially significant adverse effects and the cost of treatment.<sup>6</sup>
  - iii. Given the different inclusion criteria for the pirfenidone trials, these results may not be applicable to patients with IPF with more severe impairment.<sup>6</sup>
  - iv. The evidence does not suggest optimal duration of therapy, and it is unknown how long the treatment effect endures with ongoing therapy.<sup>6</sup>
- c. Antacids (very low confidence in effect estimates).
  - i. Background: gastroesophageal reflux disease (GERD) has been observed in up to 90% of patients with IPF. GERD is a risk factor for aspiration or microaspiration which could subsequently cause pneumonitis and has been postulated to cause or worsen IPF. Antacid use on a regular basis with proton pump inhibitors (PPI) or histamine-2 receptor antagonists (H2RA) may decrease risk for microaspiration-associated lung injury.<sup>6</sup>
  - ii. An aggregate analysis of 3 RCTs of different pharmacological treatments on patient with IPF compared patients enrolled in the trials who were on a PPI/H2RA at baseline versus patients who were not on an antacid at baseline. The analysis showed a smaller decrease in FVC during the study period for those receiving antacid treatment at baseline (MD, 0.07 L; 95% CI, 0 to 0.14 L;  $p=0.05$ ). A retrospective analysis of longitudinal cohorts suggested an association with survival for IPF patients who received antacids (hazard ratio [HR] 0.47; 95% CI, 0.24 to 0.93).<sup>6</sup>

- iii. This recommendation places higher value on possible improved lung function and survival and the low cost of therapy and a lower value on the potential adverse effects of antacids (e.g., pneumonia).<sup>6</sup>

3. The recommendation **against** the use of the following agents for the treatment of IPF is **conditional**:

- a. Phosphodiesterase-5 inhibitor (sildenafil) (moderate confidence in effect estimates).<sup>6</sup>
  - i. Sildenafil has been studied in 2 RCTs of patients with IPF. One placebo-controlled trial did not find a benefit with sildenafil on the primary outcome, which was the proportion of patients who showed more than 20% improvement in the 6MWD after 12 weeks of treatment. A pre-defined subgroup analysis of patients with documented right ventricular hypertrophy or right ventricular systolic dysfunction did find improvement in the primary outcome (mean distance, 99.3 m; 95% CI, 22.3 to 176.2 m). A second, smaller trial, which excluded patient with known pulmonary hypertension or right ventricular dysfunction, also did not find benefit with sildenafil on the 6MWD test. Pooled analysis of these two trials showed no benefit of sildenafil on mortality (RR 0.51; 95% CI, 0.1 to 2.72; low confidence) or acute exacerbation (RR 0.51; 95% CI, 0.04 to 3.22; low confidence).<sup>6</sup>
  - ii. The committee felt there was a net harm with sildenafil therapy in IPF patients.<sup>6</sup>
- b. Endothelin receptor antagonists (ERA) (macitentan, bosentan) (low confidence in effect estimates).<sup>6</sup>
  - i. Two RCTs examined the effect of bosentan versus placebo, whereas a single RCT tested macitentan versus placebo. In the first bosentan trial, no benefit was seen in mortality (RR 1.14; 95% CI, 0.24 to 5.54), although the data suggested potential improvement, which was not statistically significant, in the composite outcome of mortality and disease progression (RR 0.62; 95% CI, 0.37 to 1.05), as measured by PFTs or clinical status. A larger, follow-up study evaluated patients with biopsy-proven interstitial pneumonia, a pathologic diagnosis consistent with IPF. Despite these modifications in study design, bosentan did not show an effect on mortality (RR 1.25; 95% CI, 0.53 to 2.96) or disease progression (RR 0.86; 95% CI, 0.71 to 1.05). In a trial that evaluated macitentan, no difference was seen in patients treated with macitentan versus those who received placebo in mortality (RR 0.74; 95% CI, 0.13 to 4.33), mortality or disease progression (RR 1.02; 95% CI, 0.63 to 1.66), or change in FVC (MD 0.00; 95% CI, -0.16 to 0.16).<sup>6</sup>
  - ii. This recommendation places relatively higher value on clinically meaningful outcomes and high cost of this medication and a relatively lower value on possible reduction of the risk of mortality or disease progression. Given the inconsistency of a composite outcome (mortality or disease progression) across trials and the imprecision in the estimate of effect, the committee recommended against this therapy.<sup>6</sup>
- c. N-acetylcysteine monotherapy (inhaled and oral) (low confidence in effect estimates).<sup>6</sup>
  - i. A pooled analysis of 3 RCTs that examined NAC monotherapy in patients with IPF did not demonstrate statistically significant differences in mortality (RR 1.97; 95% CI, 0.50 to 7.71; low confidence), in change in FVC (high confidence), quality of life (moderate confidence), or adverse outcomes (low confidence). Two studies reported on 6-minute walk test distance and a statistically significant improvement was seen with NAC monotherapy (MD, 44.33 meters; 95% CI, 2.92 to 85.75; very low confidence).<sup>6</sup>
  - ii. This recommendation places higher value on the potential risks, inconvenience of use, and cost of therapy and low value on possible improvement of outcomes with unclear clinical significance. The committee did not find sufficient evidence for differences in outcomes between inhaled versus oral administration on NAC, and so this recommendation applies to both interventions.<sup>6</sup>

In summary, the committee did not provide strong recommendations for use of any drug in IPF, although pirfenidone and nintedanib, which are the only currently approved drugs for IPF, received a conditional recommendation for use with moderate confidence in effect estimates.<sup>6</sup> No suggestions for or against combination regimens or sequential therapies were provided, excluding the recommendation against using prednisone in combination with azathioprine and N-acetylcysteine.<sup>6</sup>

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Two additional guidelines for treatment of IPF were excluded due to poor quality.<sup>13,30</sup>

### **New Formulations or Indications:**

#### *Nintedanib: New Indication for Systemic Sclerosis-Associated Interstitial Lung Disease (9/6/2019)*

Nintedanib was studied in a phase 3, multi-centered, randomized, double-blind, placebo-controlled, parallel-group trial in which 576 adult patients with systemic sclerosis and interstitial lung disease with fibrosis affecting more than 10% of the lungs received nintedanib 150 mg twice daily (n=288) or placebo (n=288) for at least 52 weeks.<sup>8</sup> Patients were required to have an FVC that was at least 40% of the predicted value and a DLCO that was 30 to 89% of the predicted value.<sup>8</sup> Patients with pulmonary hypertension were excluded.<sup>8</sup> The study was funded by Boehringer Ingelheim, the manufacturer of nintedanib.<sup>8</sup> All analyses were conducted in the patients who received at least one dose of the trial drug or placebo.<sup>8</sup> About half the patients had diffuse cutaneous systemic sclerosis, and half had limited cutaneous systemic sclerosis.<sup>8</sup> The median time since the onset of the first non-Raynaud's symptom was 3.4 years.<sup>8</sup> The mean age of the patients was 54.0 years, and the mean FVC and DLCO were 72.5% and 53.0% of the predicted value, respectively.<sup>8</sup> Among the patients who received at least one dose, 232 (80.6%) in the nintedanib group and 257 (89.2%) in the placebo group completed the 52-week intervention.<sup>8</sup>

The primary end point was the annual rate of decline in the FVC (mL/year), as assessed over the 52-week period.<sup>8</sup> Key secondary endpoints were absolute changes from baseline in the modified Rodnan skin score and the SGRQ total score at week 52.<sup>8</sup> Background information on the SGRQ was mentioned earlier in this class update.<sup>8</sup> The modified Rodnan skin score is used to evaluate a patient's skin thickness through palpation of 17 areas; scores range from 0 to 3 for each area (to give a maximum score of 51), with higher scores indicating worse skin fibrosis.<sup>8</sup> The minimal clinically important difference in modified Rodnan skin score in patients with ILD associated with systemic sclerosis has not been established but has been suggested to be 3 to 4 points.<sup>8</sup> Other secondary endpoints included the annual rate of decline in FVC and DLCO as a percentage of the predicted value and absolute changes in FVC from baseline to week 52.<sup>8</sup>

For the primary endpoint, the annual rate of change in FVC over a 52-week period was lower in the nintedanib group than in the placebo group (-52.4 mL/year vs. -93.3 mL/year; difference, 41.0 mL/year; 95% CI, 2.9 to 79.0; p=0.04).<sup>8</sup> Multiple-imputation sensitivity analyses for missing data yielded p-values ranging from 0.06 to 0.10.<sup>8</sup> The mean absolute change from baseline in FVC at week 52 was -54.6 mL in the nintedanib group and -101.0 mL in the placebo group (difference, 46.4 mL; 95% CI, 8.1 to 84.7).<sup>8</sup> The mean absolute change from baseline in the modified Rodnan skin score at week 52 was -2.17 in the nintedanib group and -1.96 in the placebo group (difference, -0.21; 95% CI, -0.94 to 0.53).<sup>8</sup> The mean absolute change from baseline in total score on the SGRQ at week 52 was 0.81 in the nintedanib group and 0.88 in the placebo group (difference, 1.69; 95% CI, -0.73 to 4.12).<sup>8</sup> These key secondary endpoints also did not differ between the groups based on different baseline characteristics.<sup>8</sup> The percentages of patients with any adverse event and any serious adverse event were similar in the nintedanib group and placebo group; however, the percentage of patients who had an adverse event that led to the discontinuation of the assigned intervention was higher in the nintedanib group than in the placebo group (16.0% vs. 8.7%).<sup>8</sup> Over the entire trial period, 10 patients (3.5%) in the nintedanib group and 9 patients (3.1%) in the placebo group died (HR 1.16; 95% CI, 0.47 to 2.84).<sup>8</sup>

Nintedanib obtained an expanded indication by the FDA in September 2019 to slow the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease.<sup>7</sup> This is the second indication for nintedanib, which was already approved treatment of IPF.

## *Nintedanib: New Indication for Treatment for Chronic Fibrosing Interstitial Lung Diseases with a Progressive Phenotype (3/9/2020)*

Nintedanib was studied in a phase 3, multi-centered, randomized, double-blind, placebo-controlled trial in which 663 adult patients with physician-diagnosed fibrosing interstitial lung disease received nintedanib 150 mg twice daily (n=332) or placebo (n=331) for at least 52 weeks.<sup>9</sup> Because nintedanib already had an indication for IPP, efforts were made to enroll patients with a progressive fibrotic phenotype other than IPF.<sup>9</sup> The study was funded by Boehringer Ingelheim, the manufacturer of nintedanib. Mean age of patients was 69 years and mean FVC was 69.0% of the predicted value.<sup>9</sup> Overall, 252 patients (75.9%) in the nintedanib group and 282 (85.2%) in the placebo group completed 52 weeks of treatment.<sup>9</sup> A total of 80 patients prematurely discontinued nintedanib (65 patients due to an adverse event) and a total of 49 patients prematurely discontinued placebo (34 patients due to an adverse event).<sup>9</sup> All analyses were conducted in the patients who received at least one dose of the trial drug or placebo.<sup>9</sup> The analysis was based on all data measurements obtained over the 52-week period, including those from patients who had discontinued nintedanib or placebo.<sup>9</sup> The mean duration of exposure over 52 weeks was 10.3 months in the nintedanib group and 11.2 months in the placebo group.<sup>9</sup>

The primary end point was the annual rate of decline in the FVC, as assessed over the 52-week period.<sup>9</sup> The secondary endpoints were the absolute change from baseline in the total score on the K-BILD questionnaire at week 52, the time until the first acute exacerbation of interstitial lung disease or death over the 52-week period, and the time until death over the 52-week period.<sup>9</sup> The K-BILD questionnaire is a self-administered health-status questionnaire that has been developed in patients with interstitial lung diseases.<sup>9</sup> It consists of 15 items in 3 domains: breathlessness and activities, psychological factors, and chest symptoms.<sup>9</sup> Domain and total scores range from 0 to 100, with higher scores representing better health status.<sup>9</sup> The minimal clinically important difference has not been established, but a change of between 4 and 8 points has been suggested to represent a meaningful change.<sup>9</sup>

For the primary endpoint, the adjusted rate of decline in the FVC over the 52-week period was -80.8 mL per year in the nintedanib group and -187.8 mL per year in the placebo group (between-group difference, 107.0 mL; 95% CI, 65.4 to 148.5; p<0.001).<sup>9</sup> At week 52, the adjusted mean absolute change from baseline in the total score on the K-BILD questionnaire was 0.55 points in the nintedanib group and -0.79 points in the placebo group (between-group difference, 1.34 points; 95% CI, -0.31 to 2.98).<sup>9</sup> The percentage of patients who either died or had an acute exacerbation of interstitial lung disease over the 52-week period was 7.8% in the nintedanib group and 9.7% in the placebo group (HR 0.80; 95% CI, 0.48 to 1.34).<sup>9</sup> The percentage of patients who died over the 52-week period was 4.8% in the nintedanib group and 5.1% in the placebo group (HR 0.68; 95% CI, 0.32 to 1.47).<sup>9</sup>

A greater percentage of patients in the nintedanib group than in the placebo group had adverse events leading to a permanent dose reduction (33.1% vs. 4.2%) and to discontinuation of either nintedanib or placebo (19.5% vs. 10.3%).<sup>9</sup> Fatal adverse events were less frequent in the nintedanib group than in the placebo group (3.3% vs. 5.1%).<sup>9</sup> The most frequent adverse event was diarrhea, which was reported in 222 patients (66.9%) in the nintedanib group and in 79 patients (23.9%) in the placebo group.<sup>9</sup>

Nintedanib obtained an expanded indication by the FDA in March 2020 to slow the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease.<sup>7</sup> This is the third indication for nintedanib, which was already approved treatment of IPF and patients with systemic sclerosis-associated interstitial lung disease.

### **New FDA Safety Alerts:**

**Table 2.** Description of new FDA Safety Alerts.

Author: Gibler

Date: June 2020

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Nintedanib	OFEV	9-6-19	Warnings and Precautions	Elevated Liver Enzymes and Drug-induced Liver Injury
Pirfenidone	ESBRIET	7-31-19	Warnings and Precautions	Elevated Liver Enzymes and Drug-induced Liver Injury

Nintedanib:

Warnings and Precautions: Elevated Liver Enzymes and Drug-Induced Liver Injury (9/6/2019):<sup>7,10</sup>

Cases of drug-induced liver injury have been observed with nintedanib. In the clinical trials and post-marketing experience, serious and non-serious cases of drug-induced liver injury, including fatal severe liver injury, have been reported. Most hepatic events occur within the first 3 months of treatment. In clinical trials, administration of nintedanib was associated with elevations of liver enzymes (ALT, AST, ALKP, GGT) and bilirubin. Liver enzyme and bilirubin increases were reversible with dose modification or interruption in most cases. In IPF studies, most (94%) patients with ALT or AST elevations had elevations less than 5-times upper limit of normal (ULN) and most (95%) patients with bilirubin elevations had elevations less than 2-times ULN. In the SSc-ILD study, a maximum ALT or AST greater than or equal to 3-times ULN was observed for 4.9% of patients in the nintedanib group and for 0.7% of patients in the placebo group. Patients with a low body weight (less than 65 kg), Asian, and female patients may have a higher risk of elevations in liver enzymes. Nintedanib exposure increased with patient age, which may also result in a higher risk of increased liver enzymes.

Drug Interactions: Pirfenidone (11/9/2018)<sup>7,10</sup>

In a multiple-dose study conducted to assess the pharmacokinetic effects of concomitant treatment with nintedanib and pirfenidone, the coadministration of nintedanib with pirfenidone did not alter the exposure of either drug. Therefore, no dose adjustment is necessary during concomitant administration of nintedanib with pirfenidone.

Pirfenidone:

Warnings and Precautions: Elevated Liver Enzymes and Drug-Induced Liver Injury (7/31/2019)<sup>10,31</sup>

Cases of drug-induced liver injury have been observed with pirfenidone. In post-marketing experience, serious and non-serious cases of drug-induced liver injury, including fatal severe liver injury, have been reported. Conduct baseline liver function tests (ALT, AST, and bilirubin) prior to the initiation of pirfenidone, monthly for the first 6 months, every 3 months thereafter, and as clinically indicated. Measure liver function tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. Dosage modification or interruption may be necessary for liver enzyme elevations.

## Randomized Controlled Trials:

**Table 3.** Key Inclusion Criteria for Randomized Controlled Trials.

Population	Idiopathic Pulmonary Fibrosis
Intervention	Nintedanib, pirfenidone
Comparator	Other active drug (e.g., nintedanib, pirfenidone, sildenafil, n-acetylcysteine, etc.)
Outcomes	Mortality, morbidity outcomes, symptoms, quality of life or functioning. Surrogate markers of lung function acceptable if validated (e.g., forced vital capacity; carbon monoxide diffusing capacity)
Timing	Multi-week study or longer
Setting	Outpatient

A total of 83 citations were manually reviewed from the initial literature search. After further review, 82 citations were excluded because of wrong study design (e.g., observational, post-hoc analysis), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining trial is summarized in the table below. Full abstract is included in **Appendix 2**.

**Table 4.** Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Kolb, et al. <sup>5</sup>  DB, PG, RCT  N=274  13 countries  Funded by Boehringer Ingelheim	1. Nintedanib 150 mg PO BID + sildenafil 20 mg PO TID  2. Nintedanib 150 mg PO BID + Placebo PO TID  1:1  24 weeks	-Age ≥40 y -IPF diagnosis -Recent chest CT and surgical lung biopsy specimens consistent with IPF diagnosis -Single-breath DLCO ≤35% of predicted value	Change from baseline in the SGRQ total score at week 12  <i>SGRQ: A 50-item questionnaire divided into 3 domains (impact, symptoms, activity) that assess health-related QoL in patients with respiratory disease. Total scores range from 0-100, with higher scores indicated worse QOL. The likely MCID for patients with IPF is a change of ≥4 points.<sup>5</sup></i>	Week 12: 1. -1.28 points 2. -0.77 points  MD -0.52 points (95% CI, -3.33 to 2.30 points)  Week 24: 1. 0.23 points 2. 2.42 points  MD -2.19 points (95% CI, -5.40 to 1.02 points)  Conclusion: In patients with advanced IPF and DLCO ≤35% of the predicted value, nintedanib plus sildenafil did not provide a significant benefit as compared with nintedanib alone.

Abbreviations: BID = twice daily; DB = double blind; CI = confidence interval; CT = computed tomography; DLCO = diffusing capacity of the lung for carbon monoxide; FVC = forced vital capacity; IPF = idiopathic pulmonary fibrosis; MCID = minimal clinically important difference; MD = mean difference; PC = placebo controlled; PG = parallel group; PO = by mouth; QoL = quality of life; RCT = randomized clinical trial; SGRQ = St. George's Respiratory Questionnaire; TID = three times daily.

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## Appendix 1: Current Preferred Drug List

<u>Generic</u>	<u>Brand</u>	<u>Form</u>	<u>PDL</u>
nintedanib esylate	OFEV	CAPSULE	N
pirfenidone	ESBRIET	CAPSULE	N
pirfenidone	ESBRIET	TABLET	N

## Appendix 2: Abstracts of Comparative Clinical Trials

**BACKGROUND:** Nintedanib is an approved treatment for idiopathic pulmonary fibrosis (IPF). A sub- group analysis of a previously published trial suggested that sildenafil may provide benefits regarding oxygenation, gas exchange as measured by the diffusion capacity of the lungs for carbon monoxide (DLCO), symptoms, and quality of life in patients with IPF and severely decreased DLCO. That idea was tested in this trial.

**METHODS:** We randomly assigned, in a 1:1 ratio, patients with IPF and a DLCO of 35% or less of the predicted value to receive nintedanib at a dose of 150 mg twice daily plus sildenafil at a dose of 20 mg three times daily (nintedanib-plus-sildenafil group) or nintedanib at a dose of 150 mg twice daily plus placebo three times daily (nintedanib group) for 24 weeks. The primary end point was the change from baseline in the total score on the St. George's Respiratory Questionnaire (SGRQ) at week 12 (the total score ranges from 0 to 100, with higher scores indicating worse health-related quality of life). Secondary end points included measures of dyspnea and safety.

**RESULTS:** A total of 274 patients underwent randomization. There was no significant difference in the adjusted mean change from baseline in the SGRQ total score at week 12 between the nintedanib-plus-sildenafil group and the nintedanib group (−1.28 points and −0.77 points, respectively; p=0.72). A benefit from sildenafil treatment was not observed with regard to dyspnea as measured with the use of the University of California, San Diego, Shortness of Breath Questionnaire. No new safety signals were observed, as compared with previous trials.

**CONCLUSIONS:** In patients with IPF and a DLCO of 35% or less of the predicted value, nintedanib plus sildenafil did not provide a significant benefit as compared with nintedanib alone. No new safety signals were identified with either treatment regimen in this population of patients. (Funded by Boehringer Ingelheim; INSTAGE ClinicalTrials.gov number, NCT02802345.)

## Appendix 3: Medline Search Strategy

- 1 *exp Idiopathic Pulmonary Fibrosis/ 3587*
- 2 *nintedanib.mp. 822*
- 3 *pirfenidone.mp. 1158*
- 4 *2 or 3 1670*
- 5 *1 and 4 503*
- 6 *limit 5 to (english language and yr="2015 -Current" and (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 observational study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review" or systematic reviews as topic)) 83*

## Drugs for Interstitial Lung Disease~~Idiopathic Pulmonary Fibrosis (IPF)~~ Agents

**Goal:**

- Restrict use to populations with chronic interstitial lung disease in which the drugs have demonstrated efficacy with FDA approval.

**Length of Authorization:**

- Up to 12 months

**Requires PA:**

- Non-preferred drugs

**Preferred Alternatives:**

- No preferred alternatives at this time

Table 1. FDA-approved Indications.

Indication	Nintedanib	Pirfenidone
<u>Idiopathic pulmonary fibrosis</u>	X	X
<u>Chronic fibrosing interstitial lung disease with a progressive phenotype</u>	X	
<u>Systemic sclerosis-associated interstitial lung disease</u>	X	

Approval Criteria		
<del>1. Is this request for continuation of therapy previously approved by the FFS program (patient has already been on IPF drug)?</del>	<del>Yes: Go to <b>Renewal Criteria</b></del>	<del>No: Go to #2</del>
<del>2. Does the patient have a diagnosis of idiopathic pulmonary fibrosis <u>Is the</u></del>	<del>Yes: Go to #<u>23</u></del>	<del>No: Pass to RPh. Deny; medical appropriateness.</del>

<u>claim for a drug with an FDA-approved interstitial lung disease indication as outlined in Table 1?(ICD-10 J84112)?</u> <del>3.1.</del>		
<u>4.2.</u> Is the treatment prescribed by a pulmonologist?	<b>Yes:</b> Go to # <u>34</u>	<b>No:</b> Pass to RPh. Deny; medical appropriateness.
<del>5.</del> <del>Does the patient have a forced vital capacity (FVC) &gt;50%?</del>	<del><b>Yes:</b> Go to #5</del>	<del><b>No:</b> Pass to RPh. Deny; medical appropriateness.</del>
<u>6.3.</u> Is the patient a current smoker?	<b>Yes:</b> Pass to RPh. Deny; medical appropriateness.  Efficacy of approved drugs for IPF may be altered in smokers due to decreased exposure (see prescribing information).	<b>No:</b> <u>Approve for up to 12 months.</u> <del>Go to #6</del>
<del>7.</del> <del>Are pirfenidone and nintedanib concurrently prescribed in this patient?</del>	<del><b>Yes:</b> Pass to RPh. Deny; medical appropriateness. Safety and efficacy of concomitant therapy has not been established.</del>	<del><b>No:</b> Approve for up to 12 months.</del>

### Renewal Criteria

<del>Is there evidence of disease progression (defined as <math>\geq 10\%</math> decline in percent-predicted FVC) within the previous 12 months?</del>	<del><b>Yes:</b> Pass to RPh. Deny; medical appropriateness.</del>	<del><b>No:</b> Approve for up to 12 months.</del>
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P&T/DUR Review: 6/20 (AG): 7/15  
Implementation: TBD, 8/16, 8/25/15

## Drug Class Update with New Drug Evaluation: Oral Cystic Fibrosis Modulators

**Date of Review:** June 2020

**Date of Last Review:** September 2019 (PA update)

**Generic Name:** elexacaftor /tezacaftor/ivacaftor

**Dates of Literature Search:** 08/01/2018 – 01/31/2020

**Brand Name (Manufacturer):** Trikafta® (Vertex)

**Dossier Received:** Yes

**Current Status of PDL Class:**

See **Appendix 1**.

### **Purpose for Class Update:**

The purpose of this class update is to evaluate new evidence for the safety and effectiveness of oral cystic fibrosis (CF) modulators in reducing respiratory symptoms or pulmonary exacerbations associated with CF and improving quality of life, as well as to evaluate the evidence and place in therapy of elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA).

### **Research Questions:**

1. What is the comparative evidence for oral CF modulators in improving clinically important outcomes such as respiratory symptoms, pulmonary exacerbations, mortality and quality of life in children and adults with CF? If comparative evidence remains insufficient, does any new evidence change previous conclusions regarding the effectiveness or efficacy of the CF modulators?
2. What are the comparative harms of oral CF modulators in patients being treated for CF? If comparative evidence remains insufficient, does any new evidence change previous conclusions regarding the safety of the CF modulators?
3. Are there subpopulations of patients with CF based on a specific gene mutation, disease severity, race, age, or sex, for which one of the oral CF modulators are more effective or associated with greater harm than other populations?

### **Conclusions:**

- There is insufficient evidence that the oral CF transmembrane conductance regulator (CFTR) modulators (potentiators and correctors), improve survival and overall health-related quality of life (other than the respiratory domain).<sup>1,2</sup>
- For subjects with CF homozygous for the F508del mutation, there is moderate evidence of no significant difference in quality of life (CFQ-R) for the respiratory domain or lung function between ivacaftor (IVA) and placebo.<sup>3</sup> There is moderate quality evidence of an improvement in lung function, as measured by the percent predicted forced expiratory volume in one second (ppFEV1) change from baseline with tezacaftor/ivacaftor (TEZ/IVA) and lumacaftor/ivacaftor (LUM/IVA) compared to placebo.<sup>1</sup> There is also moderate quality evidence of a decrease in pulmonary exacerbations for both LUM/IVA hazard ratio (HR) 0.61 (95% CI 0.49 to 0.76) and TEZ/IVA (HR 0.64; 95% CI 0.46 to 0.89) compared to placebo.<sup>1</sup>

- There is moderate strength evidence that IVA alone provides no respiratory benefit in those with R177H rotation.<sup>3</sup>
- There is moderate quality evidence that elxacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) improves ppFEV1 from baseline to week 4 compared to placebo in those heterozygous for the F508del mutation and a second minimal function mutation with a least squares (LS) mean treatment difference of 13.8% (95% CI 12.1 to 15.4).<sup>4</sup> There is low quality evidence of a decrease in pulmonary exacerbations through week 24 (rate ratio 0.37; 95% CI 0.25 to 0.55) in this population.<sup>4</sup>
- There is low quality evidence that ELX/TEZ/IVA improves respiratory function compared to TEZ/IVA in those homozygous for the F508del mutation with a change from baseline in ppFEV1 at week 4 of 10.4% with ELX/TEZ/IVA and 0.4% with TEZ/IVA (LS mean difference 10%; 95% CI 7.4 to 12.6).<sup>5</sup> There is insufficient evidence that ELX/TEZ/IVA improves pulmonary exacerbations compared to TEZ/IVA in this population.
- There is insufficient clinical data in many of the uncommon CFTR mutations that are included in the FDA approved indication of ELX/TEZ/IVA.
- There is insufficient data on the long-term safety of ELX/TEZ/IVA. There are safety concerns regarding the side effects of elevations in liver transaminases and bilirubin, rhabdomyolysis, elevated creatinine kinase, and rash. More data are needed to assess the long-term safety of ELX/TEZ/IVA.

#### Recommendations:

- Maintain ELX/TEZ/IVA as non-preferred and add to clinical prior authorization criteria (**Appendix 5**).
- Update prior authorization criteria for initial approval of 6 months and 12 months for subsequent approval (**Appendix 5**).

#### Summary of Prior Reviews and Current Policy

- There is low quality evidence that TEZ/IVA modestly improves lung function, decreases pulmonary exacerbations and improves respiratory domain quality of life in those with CF homozygous for the F508del mutation
- There is insufficient evidence that TEZ/IVA has a significant effect on clinical outcomes for the treatment of CF in those heterozygous for the F508del mutation and a second allele predicted to have residual function.
- There is moderate quality evidence that IVA is effective in patients with the G551D mutation. There is insufficient evidence that IVA monotherapy has a clinically relevant impact on other mutations.
- There is insufficient evidence that lumacaftor/ivacaftor (LUM/IVA) has a significant effect on clinically important outcomes for the treatment of CF in those homozygous for the F508del mutation on the CFTR gene. It was associated with only an absolute 2.8% improvement in FEV1 (estimated by averaging the absolute change at weeks 16 and 24) and a nominal decrease in pulmonary exacerbations compared to placebo.
- There is insufficient evidence that LUM/IVA improves lung function in children ages 6 to 11 years old with CF homozygous for the F508del mutation. Approval was based on a phase 3 study evaluating nonclinical outcomes.
- LUM/IVA has not demonstrated a significant effect on FEV1 in patients who are heterozygous for the F508del mutation and therapy should not be used in this patient population.
- Evidence limitations:
  - Evidence remains insufficient to compare the efficacy/effectiveness or safety of CF modulators against standard of care including dornase alfa and hypertonic saline.
  - Evidence remains insufficient to determine the effects of oral CF modulators on long term disease progression or to know if TEZ/IVA is effective in patients with very severe CF (ppFEV1 <40%) or very mild CF (ppFEV1 >90%).
  - Evidence remains insufficient to determine appropriate criteria for discontinuing oral CF modulators for lack of effectiveness.

- There is significant involvement from the manufacturer in all clinical trials of IVA, LUM/IVA and TEZ/IVA including but not limited to: funding, study design, data collection analysis and interpretation as well as writing and publication of the manuscript.

**Background:**

Cystic Fibrosis (CF) is an autosomal recessive condition that can affect multiple organs, of which progressive lung disease is responsible for approximately 85% of mortality observed in this population.<sup>6</sup> Most available treatments for CF focus on symptom management and treatment of chronic infection, including antibiotics, dornase alfa, inhaled hypertonic saline, inhaled corticosteroids, oral nonsteroidal anti-inflammatory drugs, and inhaled bronchodilators.<sup>7</sup> CF is caused by mutations in the CFTR gene. CFTR proteins are found on the surface of cells in a variety of tissues where it functions as a regulator of the chloride ion channel.<sup>8</sup> CFTR mutations are often categorized according to their functional impact on CFTR protein synthesis or function (**Table 1**). Over 1900 mutations have been identified in the CFTR gene, with different protein defects resulting from the mutation.<sup>9</sup> The F508del mutation results in misprocessing of CFTR resulting in failure of CFTR to travel to the cell surface, while the G551D and other gating mutations result in failure of CFTR protein channels to open at the cell surface. Lastly, the R117H mutation affects chloride conductance in the pore region of the channel leading to poor conductance of chloride ions.<sup>9</sup> There are three common alleles at the poly-T locus of the R117H gene (5T, 7T, 9T), with the 5T variant associated with greater severity of CF.<sup>10</sup> Of the various clinical symptoms of CF, only pancreatic function has been shown to correlate well with CFTR genotype. The most common CFTR mutation is the F508del (Class II mutation), which carries the most severe prognosis.<sup>11</sup> In the United States, approximately 90% of CF patients carry at least one allele and 50% are homozygous for the F508del mutation. In contrast, approximately 5% of those with CF exhibit residual CFTR ion transport. These residual function mutations cause disease with a more delayed onset than more common forms.<sup>12</sup>

**Table 1: CFTR mutation categories<sup>13</sup>**

Class	Description	Prevalence	Examples
Class I: protein production mutations	No functional CFTR created	22%	NA
Class II: protein processing mutations	CFTR protein created, but misfolded, keeping it from reaching the cell surface	88%	F508del
Class III: gating mutations	CFTR protein created and reaches cell surface, but does not function properly	6%	G551D
Class IV: conduction mutations	Opening in CFTR protein ion channel is faulty	6%	R117H
Class V: insufficient protein mutations	CFTR created in insufficient quantities	5%	

Clinically meaningful outcomes of CF treatment include mortality, frequency of pulmonary exacerbations, quality of life and respiratory symptoms. Forced expiratory volume in one second (FEV<sub>1</sub>) is a commonly used surrogate outcome in clinical trials. A minimal clinically important difference for FEV<sub>1</sub> has not been defined or agreed upon because of the heterogeneous nature of the condition.<sup>14</sup> According to National Institute of Clinical Excellence (NICE), an absolute change in ppFEV<sub>1</sub> of 5% or more would be considered clinically important.<sup>14</sup> Changing the FEV<sub>1</sub> rate of decline would be the most meaningful effect, but would require a long study duration. In CF patients, FEV<sub>1</sub> decreases on average by 1-3% per year but varies based on age and baseline lung function.<sup>15</sup> In CF patients with moderate to severe lung disease, inhaled tobramycin and dornase alfa have shown improvement in FEV<sub>1</sub> ranging from 7.8%-12% with inhaled tobramycin and 5.8%-7.3% with dornase alfa.<sup>16</sup> There is also fair evidence to suggest that macrolide antibiotics provide benefit for all levels of disease with improvements in FEV<sub>1</sub> from 3.6%-6.2%.<sup>16</sup> The Cystic Fibrosis Questionnaire-revised (CFQ-R) is a validated patient-reported outcome questionnaire specific to CF which focuses on health perception, quality of life, and clinically relevant respiratory symptoms. A minimally clinically important difference of 4 points was established for the respiratory symptom domain.<sup>17</sup> Change in body mass index (BMI) is also a commonly measured secondary outcome in trials of CF children, as studies have shown that lower than average birth weights and poor growth are correlated with poorer lung function, and increased morbidity and mortality.<sup>17</sup> The nutritional status of patients with CF is strongly associated with pulmonary function, respiratory status, and survival. Sweat chloride level is the gold standard for a

diagnosis of CF. Normal individuals typically have levels less than 40 mmol/L, but patients with CF have elevated levels greater than 60 mmol/L.<sup>16</sup> More recently, endpoints such as sweat chloride, nasal potential difference, and the intestinal current measurement are proposed surrogate markers of CFTR function, as these reflect sodium absorption and chloride secretion dependent on CFTR function.<sup>9</sup> Sweat chloride has been used as a biomarker for evaluation of change in CFTR activity in clinical trials of IVA.<sup>18</sup> Although initial studies showed a reduction in the sweat chloride levels to values below the diagnostic threshold for CF (60 mmol/L), there is no evidence that sweat chloride is correlated with meaningful clinical benefits, and it has not shown to correlate with improvement in FEV<sub>1</sub>.<sup>16</sup> Clinical severity of CF is dependent on other factors in addition to CFTR function, and what aspect of CFTR function is affected depends on the specific combination of mutations in the individual.

FDA approved oral agents intended to enhance mutant CFTR protein function are included in Table 2.<sup>18</sup> Ivacaftor (IVA) is a CFTR potentiator indicated for the management of CF in patients at least 6 months of age who have one of 38 CFTR mutations shown to be responsive to IVA based on clinical and/or in vitro assay data (**Table 2**).<sup>19</sup> The most common gating mutation, G551D, represent approximately 7% of the U.S. CF population.<sup>18</sup> In trials of patients with the G551D mutation, IVA resulted in an increased FEV<sub>1</sub> by an absolute value of 10.6% compared to placebo through week 24, a 26% absolute decrease in respiratory exacerbations, a reduction in sweat chloride values by 50 mmol/L, and a mean weight gain of 2.7 kg.<sup>20</sup> IVA is designed to increase the time that activated CFTR channels at the cell surface remain open.<sup>21,22</sup>

Lumacaftor (LUM), tezacaftor (TEZ) and elxacaftor (ELX) are CFTR correctors designed to improve folding of the CFTR protein and transportation to the cell surface. Previous studies of IVA did not demonstrate a clinical improvement in lung function in patients homozygous for the F508del mutation.<sup>6</sup> However, the combination of LUM/IVA was approved after phase 3 trials demonstrated its efficacy for the management of CF in patients 12 years of age and older who were homozygous for the F508del mutation in the CFTR gene.<sup>23</sup> Phase 2 trials demonstrated lack of improvement in patients heterozygous for the F508del CFTR mutation.<sup>24</sup> It is currently FDA-approved for those age 2 years and older who are homozygous for the F508del mutation in the CFTR gene.<sup>25</sup> This patient group includes approximately 34% of the U.S. CF population.<sup>18</sup> Studies of LUM/IVA did not demonstrate clinically significant results on meaningful outcomes. It was associated with only an absolute 2.8% improvement in FEV<sub>1</sub> (estimated by averaging the absolute change at weeks 16 and 24) and a nominal decrease in pulmonary exacerbations compared to placebo (RR 0.61; 95% CI 0.49 to 0.76). However, this outcome was actually reported as the number of events per 48 weeks which is unreliable since the trial duration was 24 weeks. \ It remains unclear if the combination provides more benefit than IVA alone which was found to be deleterious in F508del homozygous adults in previous trials.

Tezacaftor (TEZ) is another CFTR corrector that was approved in combination with IVA based on two separate phase 3, randomized, double-blind trials in patients 12 years of age or older who were either heterozygous for the F508del mutation with a residual-function CFTR mutation or those homozygous for F508del.<sup>12,26</sup> It had a modest benefit on ppFEV<sub>1</sub> in those homozygous for F508del (3.4% absolute change from baseline) and a clinically insignificant improvement in absolute change from baseline in ppFEV<sub>1</sub> (mean difference 2.1%; 95% CI 1.2% to 2.9%) with TEZ/IVA compared to IVA monotherapy in patients heterozygous for the F508del mutation.

Elxacaftor (ELX) is also a CFTR corrector. It binds to a different site on the CFTR protein than other current therapies and is theorized to have an additive effect with TEZ in facilitation of cellular processing and trafficking of the F508del-CFTR to increase the amount of protein delivered to the cell surface. Triple therapy with ELX/TEZ/IVA is the most recent FDA agent approved (**Table 2**) for patients with at least one F508del mutation in the CFTR gene. Approximately 90% of individuals with CF have mutations that are eligible for treatment with ELX/TEZ/IVA.<sup>2</sup>

**Table 2: CFTR Modulators: Summary of Studied Mutations**

Generic Name (Brand)	FDA Approved Indication (in cystic fibrosis)	Specific Mutations Included
Ivacaftor <sup>19</sup> (Kalydeco®)	≥ 6 months with an ivacaftor-responsive gene mutation	E56K, G178R, S549R K1060T, G1244E, P67L, E193K, G551D, A1067T, S1251N R74W, L206W, G551S, G1069R, S1255P, D110E, R347H, D579G, R1070Q, D1270N, D110H, R352Q, S945L, R1070W G1349D, R117C, A455E, S977F, F1074L, R117H, S549N, F1052V, D1152H 3849 + 10kbc -T, 2789 +5G>A, 3272-26A-G, 711+3A-G, E831X
Lumacaftor/ivacaftor <sup>25</sup> (Orkambi®)	≥ 2 years Homozygous for F508del	Homozygous F508del
Tezacaftor/ivacaftor <sup>12,26</sup> (Symdeko®)	≥ 6 years who are homozygous for the F508del mutation OR who have at least one tezacaftor/ivacaftor-responsive CFTR mutation	Homozygous F508del, A455E, A1067T, D110E, D110H, D579G, D1152H, D1270N, E56K, E193K, E831X, F1052V, F1074L, K1060T, L206W, P67L, R74W, R1070W, R117C, R347H, R352Q, S945L, S977F, 711+3A→G, 2789+5G→A, 3272-26A→G, 3849+10kbc→T
Elexacaftor/tezacaftor/ivacaftor <sup>27</sup> (Trikafta®)	≥ 12 years who have at least one F508del mutation	See <b>Appendix 4</b>

**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:**

1. A systematic review of RCTs from the Cochrane Collaboration was done to evaluate the effects of CFTR potentiators (IVA) on clinically important outcomes in children and adults with CF.<sup>3</sup> Trials evaluating IVA in combination with CFTR correctors (TEZ and LUM) were not included in this analysis, which limits the applicability of the results. Overall, 5 RCTs were included in the analysis (n=447). All of the trials were parallel design and all of them were funded by Vertex Pharmaceuticals. Three trials included subjects with the G551D mutation, one with CF individuals homozygous for the F508del mutation, and one included those with the R117H mutation.<sup>3</sup> All of the included trials had a high risk of reporting bias due to missing data for various tertiary outcomes and/or no protocols being available. Additionally, all of the trials had unclear risk of performance bias due to insufficient information to assess appropriate blinding. Lastly, 3 trials had high risk of attrition bias since participant data was excluded from the analysis. As a result, the quality of the evidence was moderate to low.

For any of the mutations studied, there was insufficient evidence to evaluate the effects of IVA on survival, as none of the RCTs reported survival data or deaths. There was also insufficient evidence on total quality of life.<sup>3</sup> For subjects homozygous for the F508del mutation, there is moderate quality evidence of no significant difference in the respiratory domain of quality of life (CFQ-R) between IVA and placebo and no statistically significant difference ppFEV1 at 16 weeks between IVA and placebo (mean difference 2.4%; 95% CI -0.95 to 5.75).<sup>3</sup> From the study in the R117H mutation, there was moderate strength evidence of a significant improvement in CFQ-R respiratory domain score and no significant difference in ppFEV1 change from baseline. The 3 G551D trials provided moderate strength evidence of a statistically significant improvement in change in ppFEV1 from baseline. However, the data was unable to be combined due to differences in the trials. In the two adult trials with G551D, moderate strength evidence suggests a significant higher CFQ-R scores with IVA compared to placebo. However, there was no significant difference in the pediatric trial. There is low strength evidence in all genotypes of no difference in adverse events resulting in treatment discontinuation.<sup>3</sup>

Overall, there was no benefit on respiratory function or quality of life with IVA in those homozygous for the F508del mutation and no respiratory benefit seen in people with R117H. There was a statistically significant improvement in lung function in children and adults with the G551D rotation. There is insufficient evidence in all genotypes on overall survival and total quality of life.

2. Another Cochrane Collaboration systematic review evaluated the effects of CFTR correctors approved at the time (LUM and TEZ) in children and adults with Class II CFTR mutations (most commonly F508del).<sup>1</sup> RCTs comparing a CFTR corrector to placebo or another intervention were included, as well as studies when CFTR correctors are administered with the potentiator IVA. A total of 13 trials (n=2215) were included in the qualitative synthesis and 10 were included in the meta-analysis.<sup>1</sup> Twelve RCTs recruited individuals homozygous for F508del, one RCT recruited participants with one F508del mutation and a second mutation with residual function. Five studies evaluated LUM/IVA and 2 studies evaluated TEZ/IVA. Six trials had high risk of selective reporting bias, and 7 trials had unclear risk of selection bias due to unclear sequence generation and allocation concealment. There was insufficient evidence on any outcomes with monotherapy with a CFTR corrector.<sup>1</sup>

Focusing on the FDA approved combination products (TEZ/IVA and LUM/IVA), there was insufficient evidence on survival as this outcome was not reported in any of the trials. There was high quality evidence of a significant but small improvement in respiratory domain quality of life score (CVQ-R) with LUM/IVA compared to placebo (mean difference 2.62 points; 95% CI 0.64 to 4.59) and moderate quality evidence of an improvement with TEZ/IVA compared to placebo (mean difference 5 points; 95% CI 3.2 to 7.0).<sup>1</sup> There was high quality evidence of an improvement in lung function, as measured by ppFEV1 change from baseline, with LUM/IVA compared to placebo (mean difference 5.21%; 95% CI 3.61 to 6.80).<sup>1</sup> There was moderate quality evidence of a relative improvement in ppFEV1 with TEZ/IVA of 6.8% (95% CI 5.3 to 8.3) compared to placebo. There is also moderate quality evidence of a decrease in pulmonary exacerbations for both LUM/IVA (HR 0.61; 95% CI 0.49 to 0.76) and TEZ/IVA (HR 0.64; 95% CI 0.46 to 0.89) compared to placebo.<sup>1</sup>

#### **New Guidelines:**

None

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**New Formulations or Indications:**

Additional indications expanding approved age and mutations have been included in prior PA updates. No new formulations or indications have been approved since the last PA criteria update (September 2019).

**New FDA Safety Alerts:**

None

**Randomized Controlled Trials:**

Four citations were manually reviewed from the initial literature search. After further review, 2 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 2 trials are included in the new drug evaluation and summarized in the evidence table (Table 5).

**NEW DRUG EVALUATION: elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA)**

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

**Clinical Efficacy:**

ELX/TEZ/IVA was FDA approved based on two, phase 3 RCTs in two different CFTR mutation populations.<sup>4,5</sup> The primary outcome in both trials was the absolute change from baseline in ppFEV1 at week 4. Secondary outcomes included the CFQ-R respiratory domain, body mass index (BMI) (only one trial), sweat chloride, and number of pulmonary exacerbations (only one trial). The trial by Middleton et al. evaluated the efficacy of ELX/TEZ/IVA in CF patients who are heterozygous for the F508del mutation and a second minimal function mutation over 24 weeks.<sup>4</sup> A minimal function mutation makes either no CFTR protein (class I mutation) or for which in vitro data suggest the CFTR protein is not responsive to other CFTR therapies. Previous trials have not shown LUM/IVA or TEZ/IVA to be effective in this population.<sup>13</sup> Minimal function mutations detectable by an FDA assay are included in **Appendix 4**. Pulmonary exacerbations were defined as new or change in antibiotic therapy due to presence of at least 4 of the following symptoms: change in sputum, new hemoptysis, cough, dyspnea, malaise, fever, anorexia, sinus pain, sinus discharge, decrease in pulmonary function by 10%, or radiographic changes.

Overall, there was a statistically significant improvement in ppFEV1 at week 4 compared to placebo with a LS mean absolute change of 13.8 percentage points (95% CI 12.1 to 15.4;  $p < 0.0001$ ).<sup>4</sup> This was maintained through week 24 with LS mean absolute change of 14.3 percentage points (95% CI 12.7 to 15.8). Treatment with ELX/TEZ/IVA also resulted in a significant reduction in pulmonary exacerbations through week 24 with 41 total exacerbations in the ELX/TEZ/IVA arm and 113 in the placebo arm (rate ratio 0.37; 95% CI 0.25 to 0.55) as well as a significant improvement in other secondary outcomes (quality of life, BMI, sweat chloride concentration) when compared to placebo.<sup>4</sup>

There are many limitations increasing the risk of bias in this study and decreasing the applicability. It is unknown how many subjects achieved a clinically significant change in quality of life, as measured by the CFQ-R domain, and there is insufficient information to assess the severity of the exacerbations detected. Pulmonary exacerbations were reported as an annualized estimated event rate based on 48 weeks even though only 24 weeks of data is available.

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Additionally, the enrolled population only included 79 different MF mutations with the majority having a Class I mutation (78%). Therefore, clinical data is not available for all CFTR mutations in the FDA approved indication. There was a 28-day screening period prior to randomization and no information is available on how many subjects failed to meet randomization criteria during this screening period. The FDA recommended including ELX/IVA as a treatment arm to evaluate the benefit of adding a second corrector.<sup>13</sup> However, this was not included and we cannot assess the contribution of ELX or TEZ to the combination. Lastly, there was a difference of 5% or greater between the treatment arms in concomitant medication use for 13 medications, including inhaled sodium chloride, tobramycin and other medications.

The second trial by Heijerman et al. included only those who are homozygous for the F508del mutation.<sup>4</sup> It compared ELX/TEZ/IVA to TEZ/IVA for 4 weeks of therapy. Treatment with ELX/TEZ/IVA resulted in statistically significant improvements in ppFEV1 at week 4 compared to TEZ/IVA. The LS mean treatment difference for the ELX/TEZ/IVA group versus TEZ/IVA group for the change from baseline in ppFEV1 at week 4 was 10.0% (95% CI 7.4% to 12.6%;  $p < 0.0001$ ).<sup>5</sup> There was an absolute increase in ppFEV1 of 0.4% in the TEZ/IVA and 10.4% in the ELX/TEZ/IVA arm. This trial was too short in duration to evaluate other clinically important outcomes, including pulmonary exacerbations. There was also a significant improvement in the respiratory domain of the CFQ-R.

The trial population had a mean baseline ppFEV1 of 60.9% and CFQ-R score of 71.5 (range 0 to 100 with higher scores indicating better health). The majority of enrolled patients were colonized by *Pseudomonas aeruginosa* (65%); however, numerically more ELX/TEZ/IVA subjects (71%) were colonized with *Pseudomonas aeruginosa* than TEZ/IVA subjects (60%). There were also small imbalances between the ELX/TEZ/IVA and TEZ/IVA arms with the use of hypertonic saline (69% vs. 79%), inhaled corticosteroids (65% vs. 54%) and azithromycin (60% vs. 48%) between the 2 trial arms, respectively, increasing the risk of selection bias. Previous studies evaluating TEZ/IVA in those homozygous for F508del mutation demonstrated a 3.4% increase in ppFEV1, which is larger than the minor change of 0.4% in this trial. This trial also included a 28-day screening period followed by a 28-day run in period with TEZ/IVA, further limiting the applicability of these results to the general population.

#### **Clinical Safety:**

The most common adverse drug reactions to ELX/TEZ/IVA (occurring in  $\geq 5\%$  of patients and at a frequency higher than placebo by  $\geq 1\%$ ) are included in **Table 3**. Some type of skin related adverse event was experienced by 23% of subjects in the ELX/TEV/IVA arm, compared to 14% in the placebo arm. These reactions included rash, pruritis, and hypersensitivity reaction compared to 14% in the placebo arm.

**Table 3: Common Adverse Drug Reactions<sup>27</sup>**

Adverse Drug Reactions (Preferred Term)	TRIKAFTA N=202 n (%)	Placebo N=201 n (%)
Headache	35 (17)	30 (15)
Upper respiratory tract infection <sup>a</sup>	32 (16)	25 (12)
Abdominal pain <sup>b</sup>	29 (14)	18 (9)
Diarrhea	26 (13)	14 (7)
Rash <sup>c</sup>	21 (10)	10 (5)
Alanine aminotransferase increased	20 (10)	7 (3)
Nasal congestion	19 (9)	15 (7)
Blood creatine phosphokinase increased	19 (9)	9 (4)
Aspartate aminotransferase increased	19 (9)	4 (2)
Rhinorrhea	17 (8)	6 (3)
Rhinitis	15 (7)	11 (5)
Influenza	14 (7)	3 (1)
Sinusitis	11 (5)	8 (4)
Blood bilirubin increased	10 (5)	2 (1)

a Includes upper respiratory tract infection and viral upper respiratory tract infection  
b Includes abdominal pain, abdominal pain upper, abdominal pain lower  
c Includes: rash, rash generalized, rash erythematous, rash macular, rash pruritic

However, the short duration of these trials makes it difficult to evaluate adverse events. The severe adverse events that did occur suggest the potential for clinically significant elevations in liver transaminases and creatinine kinase abnormalities. The FDA reviewer noted that the data suggest an imbalance in elevations of liver enzymes and bilirubin in the ELX/TEZ/IVA arm compared to placebo and TEZ/IVA.<sup>13</sup> Additionally, ELX/TEZ/IVA has not been studied in patients with moderate or severe hepatic impairment. All 3 drug components are extensively metabolized by CYP3A4 and should not be used with strong inhibitors or inducers of CYP3A4.

#### Comparative Endpoints:

Clinically Meaningful Endpoints:

- 1) Survival
- 2) Quality of life
- 3) Pulmonary exacerbations
- 4) Serious adverse events
- 5) Study withdrawal due to an adverse event

Primary Study Endpoint:

- 1) Absolute change in ppFEV1 from baseline at week 4

**Table 4. Pharmacology and Pharmacokinetic Properties.**

Parameter	
Mechanism of Action	Elexacaftor and tezacaftor facilitate the cellular processing and trafficking of normal and select mutant forms of cystic fibrosis transmembrane conductance regulator (CFTR) (including F508del-CFTR) to increase the amount of mature CFTR protein delivered to the cell surface. Ivacaftor is a CFTR potentiator that facilitates increased chloride transport by potentiating the channel-open probability (or gating) of the CFTR protein at the cell surface.
Oral Bioavailability	Elexacaftor 80% Tezacaftor and Ivacaftor: Not determined
Distribution	Elexacaftor: 53.7 L, Tezacaftor: 82 L, Ivacaftor 293 L
Protein Binding	Elexacaftor > 99%, Tezacaftor and Ivacaftor: ~99%
Elimination	Elexacaftor: Urine 0.23%, feces ~87% as metabolites; Tezacaftor: urine 6.6%, feces: ~88%; Ivacaftor: urine 14%, feces 72%
Half-Life	Elexacaftor: 29.8 hours, Tezacaftor: 17.4 hours, Ivacaftor: 15 hours
Metabolism	CYP3A4/5 to active metabolites



<p>2.Middleton, et al.<sup>4</sup> Phase 3, MC, DB, AC, RCT</p>	<p>1. ELX/TEZ/IVA (200 mg QDay/200 mg QDay/150 mg BID) 2. placebo</p> <p>Following a 28-day screening period</p> <p>Duration: 24-weeks</p>	<p><b>Demographics:</b></p> <ul style="list-style-type: none"> <li>48% female</li> <li>Mean 26 y/o</li> <li>70% ≥ 18 y/o</li> <li>71% <i>Pseudomonas</i></li> <li>Baseline ppFEV1 61.4%</li> </ul> <p><b>Key Inclusion Criteria:</b></p> <ul style="list-style-type: none"> <li>≥ 12 years</li> <li>heterozygous for F508del and an MF mutation*</li> <li>FEV1 40-90%</li> <li>stable CF</li> </ul> <p><b>Key Exclusion Criteria:</b> See Heijerman et al</p>	<p><b>ITT:</b></p> <p>1. 200 2. 203</p> <p><b>PP:</b></p> <p>1. 197 2. 203</p> <p><b>Attrition:</b></p> <p>1. 4 2. 1</p>	<p><b>Primary Endpoint:</b> Absolute change in ppFEV1 at week 4</p> <p>1. 13.6% 2. -0.2%</p> <p>Difference 13.8% (95%CI 12.1 to 15.4) P&lt;0.001</p> <p><b>Secondary Endpoints:</b> Total Number of Pulmonary exacerbations (estimated event rate/year)</p> <p>1. 41 (0.37) 2. 113 (0.98) Rate Ratio 0.37 (95% CI 0.25 to 0.55) P&lt;0.001</p> <p>Number of subjects with pulmonary exacerbations:</p> <p>1. 31 (15.5%) 2. 76 (37.4%)</p>	<p>NA</p> <p>NA</p> <p>ARR 21.9%/ NNT 5</p>	<p><b>Discontinuations due to adverse effects:</b></p> <p>1. 3 (2%) 2. 0 (0%)</p> <p><b>Infective pulmonary exacerbation:</b></p> <p>1. 44 (21.8%) 2. 95 (47.3%)</p> <p><b>Serious adverse event:</b></p> <p>1. 28 (13.9%) 2. 42 (20.9%)</p>	<p><b>Risk of Bias (low/high/unclear):</b> <b>Selection Bias:</b> unclear: interactive web response system used for randomization. Some differences in baseline prior medications used and <i>P. aeruginosa</i> history <b>Performance Bias:</b> low: double-blinded to subjects and study team, double-dummy design <b>Detection Bias:</b> unclear: blinded to site monitor and study team. Unclear if centralized spirometry service used was blinded. <b>Attrition Bias:</b> low: mITT used for efficacy analysis. Very low attrition overall. <b>Reporting Bias:</b> High: Unclear how many subjects did not meet randomization criteria from screening period <b>Other Bias:</b> High: Designed by Vertex Pharmaceuticals. Vertex performed data gathering, analysis, and writing of the manuscript.</p> <p><b>Applicability:</b> <b>Patient:</b> See Heijerman et al. <b>Intervention:</b> See Heijerman et al. <b>Comparator:</b> Lack of approved CFTR modulator in this population so placebo used. However, FDA recommended an ELX/IVA treatment arm, which was not included. <b>Outcomes:</b> FEV<sub>1</sub> is a surrogate outcome. There is no agreed upon difference clinically meaningful difference and it has not been established that changes in FEV<sub>1</sub> translate to long term clinical benefits. <b>Setting:</b> Multicenter (59% in North America and 41% Europe)</p>
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**Abbreviations [alphabetical order]:** AC = active comparator; AE = adverse events; ALT = alanine aminotransferase; ARR = absolute risk reduction; AST = aspartate aminotransferase; BID = twice daily; CI = confidence interval; CF = cystic fibrosis; CFQ-R = cystic fibrosis questionnaire – revised; CFTR = cystic fibrosis transmembrane conductance regulator; CV = cardiovascular; DB = double blind; FAS = full analysis set; FEV<sub>1</sub> = forced expiratory volume in one second; G6PD = glucose-6-phosphate dehydrogenase; GFR = glomerular filtration rate; ITT = intention to treat; HTN = hypertension; IVA = IVA; LSM = least squares mean difference; MC = multicenter; MF = minimal function; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = non-significant; PC = placebo controlled; PG = parallel group; PP = per protocol; ppFEV<sub>1</sub> = percent predicted forced expiratory volume in one second; QDay = daily; RCT = randomized controlled trial; ULN = upper limit of normal; yr = year

\*Minimal Function mutations included in **Appendix 4**

## References:

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**Appendix 1: Current Preferred Drug List**

<u>Generic</u>	<u>Brand</u>	<u>Form</u>	<u>Route</u>	<u>PDL</u>
dornase alfa	PULMOZYME	SOLUTION	IH	Y
sodium chloride for inhalation	SODIUM CHLORIDE	VIAL-NEB	IH	Y
tobramycin/nebulizer	KITABIS PAK	AMPUL-NEB	IH	Y
tobramycin/nebulizer	TOBRAMYCIN	AMPUL-NEB	IH	Y
aztreonam lysine	CAYSTON	VIAL-NEB	IH	N
ivacaftor	KALYDECO	GRAN PACK	PO	N
ivacaftor	KALYDECO	TABLET	PO	N
lumacaftor/ivacaftor	ORKAMBI	GRAN PACK	PO	N
lumacaftor/ivacaftor	ORKAMBI	TABLET	PO	N
tezacaftor/ivacaftor	SYMDEKO	TABLET SEQ	PO	N
tobramycin	BETHKIS	AMPUL-NEB	IH	N
tobramycin	TOBI PODHALER	CAP W/DEV	IH	N
tobramycin	TOBI PODHALER	CAPSULE	IH	N
tobramycin in 0.225% sod chlor	TOBI	AMPUL-NEB	IH	N
tobramycin in 0.225% sod chlor	TOBRAMYCIN	AMPUL-NEB	IH	N
amikacin liposomal/neb.accessr	ARIKAYCE	VIAL-NEB	IH	

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**Appendix 2: Medline Search Strategy**

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

1 *Cystic Fibrosis Transmembrane Conductance Regulator* 8908

2 *elixacaftor.mp.* 6

3 *ivacaftor.mp.* 640

4 *lumacaftor.mp* 321

5 *tezacaftor.mp.* 61

6 *CFTR potentiators.mp.* 70

7 *CFTR correctors.mp.* 73

8 *cystic fibrosis.mp. or Cystic Fibrosis/* 5—18

9 1 or 2 or 3 or 4 or 5 or 6 or 7 9208

10 8 and 9 9171

11 limit 10 to (*English language and full text and humans and yr="2018-Current" and (clinical trial, phase III or clinical trial, phase iv or comparative study or controlled clinical trial or meta analysis or randomized controlled trial or "systematic review")*) 4

## Appendix 3: Prescribing Information Highlights

### HIGHLIGHTS OF PRESCRIBING INFORMATION

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

**TRIKAFTA™ (elixacaftor, tezacaftor and ivacaftor tablets; ivacaftor tablets), co-packaged for oral use**  
**Initial U.S. Approval: 2019**

#### INDICATIONS AND USAGE

TRIKAFTA is a combination of ivacaftor, a CFTR potentiator, tezacaftor, and elixacaftor indicated for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least one *F508del* mutation in the *CFTR* gene. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to confirm the presence of at least one *F508del* mutation. (1)

#### DOSAGE AND ADMINISTRATION

- Adults and pediatric patients aged 12 years and older:
  - Morning dose: two elixacaftor 100 mg, tezacaftor 50 mg and ivacaftor 75 mg tablets
  - Evening dose: one ivacaftor 150 mg tablet
  - Morning and evening dose should be taken approximately 12 hours apart with fat-containing food. (2.1, 12.3)
- Should not be used in patients with severe hepatic impairment. Use not recommended in patients with moderate hepatic impairment unless the benefit exceeds the risk. Reduce dose if used in patients with moderate hepatic impairment. Liver function tests should be closely monitored. (2.2, 5.1, 8.7, 12.3)
- Reduce dose when co-administered with drugs that are moderate or strong CYP3A inhibitors. (2.3, 5.3, 7.2, 12.3)

#### DOSAGE FORMS AND STRENGTHS

- Tablets: fixed dose combination containing elixacaftor 100 mg, tezacaftor 50 mg and ivacaftor 75 mg.
- Co-packaged with:
- Tablets: ivacaftor 150 mg. (3)

#### CONTRAINDICATIONS

None. (4)

#### WARNINGS AND PRECAUTIONS

- Elevated liver function tests (ALT, AST or bilirubin): Liver function tests (ALT, AST, and bilirubin) should be assessed prior to initiating TRIKAFTA,

every 3 months during the first year of treatment, and annually thereafter.

In patients with a history of hepatobiliary disease or liver function test elevations, more frequent monitoring should be considered. Dosing should be interrupted in patients with ALT or AST >5 x upper limit of normal (ULN) or ALT or AST >3 x ULN with bilirubin >2 x ULN. Following resolution of transaminase elevations, consider the benefits and risks of resuming treatment. (5.1, 6)

- Use with CYP3A inducers: Concomitant use with strong CYP3A inducers (e.g., rifampin, St. John's wort) significantly decrease ivacaftor exposure and are expected to decrease elixacaftor and tezacaftor exposure, which may reduce TRIKAFTA efficacy. Therefore, co-administration is not recommended. (5.2, 7.1, 12.3)
- Cataracts: Non-congenital lens opacities/cataracts have been reported in pediatric patients treated with ivacaftor-containing regimens. Baseline and follow-up examinations are recommended in pediatric patients initiating TRIKAFTA treatment. (5.4, 8.4)

#### ADVERSE REACTIONS

The most common adverse drug reactions to TRIKAFTA (occurring in ≥5% of patients and at a frequency higher than placebo by ≥1%) were headache, upper respiratory tract infection, abdominal pain, diarrhea, rash, alanine aminotransferase increased, nasal congestion, blood creatine phosphokinase increased, aspartate aminotransferase increased, rhinorrhea, rhinitis, influenza, sinusitis and blood bilirubin increased. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Vertex Pharmaceuticals Incorporated at 1-877-634-8789 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

#### DRUG INTERACTIONS

- Strong CYP3A inducers: Avoid co-administration. (5.2, 7.1, 12.3)
- Strong or moderate CYP3A inhibitors: Reduce TRIKAFTA dosage when co-administered. Avoid food or drink containing grapefruit. (2.3, 5.3, 7.2, 12.3)

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

**Revised: 10/2019**

#### Appendix 4: Minimal Function Mutations

Minimal Function Mutation Category		Mutation				
Class I mutations (absence of CFTR protein production)	Nonsense mutations	Q2X	L218X	Q525X	R792X	E1104X
		S4X	Q220X	G542X	E822X	W1145X
		W19X	Y275X	G550X	W882X	R1158X
		G27X	C276X	Q552X	W846X	R1162X
		Q39X	Q290X	R553X	Y849X	S1196X
		W57X	G330X	E585X	R851X	W1204X
		E60X	W401X	G673X	Q890X	L1254X
		R75X	Q414X	Q685X	S912X	S1255X
		L88X	S434X	R709X	Y913X	W1282X
		E92X	S466X	K710X	Q1042X	Q1313X
		Q98X	S489X	Q715X	W1089X	Q1330X
		Y122X	Q493X	L732X	Y1092X	E1371X
		E193X	W496X	R764X	W1098X	Q1382X
		W216X	C524X	R785X	R1102X	Q1411X
	Canonical splice mutations	185+1G→T	711+5G→A	1717-8G→A	2622+1G→A	3121-1G→A
		296+1G→A	712-1G→T	1717-1G→A	2790-1G→C	3500-2A→G
		296+1G→T	1248+1G→A	1811+1G→C	3040G→C (G970R)	3600+2insT
		405+1G→A	1249-1G→A	1811+1.6kbA→G	3850-1G→A	
		405+3A→C	1341+1G→A	1811+1643G→T	3120G→A	4005+1G→A
		406-1G→A	1525-2A→G	1812-1G→A	3120+1G→A	4374+1G→T
621+1G→T		1525-1G→A	1898+1G→A	3121-2A→G		
711+1G→T		1898+1G→C				

	Small (≤3 nucleotide) insertion/deletion (ins/del) frameshift mutations	182delI 306insA 306delTAGA 365-366insT 394delTT 442delA 444delA 457TAT→G 541delC 574delA 663delT 849delG 935delA	10/8delI 1119delA 1138insG 1154insTC 1161delC 1213delT 1259insA 1288insTA 1343delG 1471delA 1497delGG 1548delG 1609del CA	1677delIA 1782delA 1824delA 1833delT 2043delG 2143delT 2183AA→G* 2184delA 2184insA 2307insA 2347delG 2585delT 2594delGT	2711delI 2732insA 2869insG 2896insAG 2942insT 2957delT 3007delG 3028delA 3171delC 3171insC 3271delGG 3349insT 3659delC	3737delA 3791delC 3821delT 3876delA 3878delG 3905insT 4016insT 4021dupT 4022insT 4040delA 4279insA 4326delTC
	Non-small (>3 nucleotide) insertion/deletion (ins/del) frameshift mutations	CFTRdele1 CFTRdele2 CFTRdele2,3 CFTRdele2-4 CFTRdele3-10,14b-16 CFTRdele4-7 CFTRdele4-11 CFTR50kdel CFTRdup6b-10 CFTRdele11 CFTRdele13,14a CFTRdele14b-17b	CFTRdele16-17b CFTRdele17a,17b CFTRdele17a-18 CFTRdele19 CFTRdele19-21 CFTRdele21 CFTRdele22-24 CFTRdele22,23 124del23bp 602del14 852del22 991del5	1461ins4 1924del7 2055del9→A 2105-2117del13insAGAAA 2372del8 2721del11 2991del32 3121-977_3499+248del2515 3667ins4 4010del4 4209TGTT→AA		
<b>Missense and in-frame deletion mutations</b>	Missense mutations that are not responsive in vitro to tezacaftor, ivacaftor, or tezacaftor/ivacaftor	A46D <sup>†</sup> G85E R347P L467P <sup>†</sup> I507del	V520F A559T <sup>†</sup> R560T R560S A561E	Y569D <sup>†</sup> L1065P R1066C L1077P <sup>†</sup> M1101K	N1303K	

Appendix 5: Prior Authorization Criteria

**Oral Cystic Fibrosis Modulators**

**Goals:**

- To ensure appropriate drug use and limit to patient populations in which they have demonstrated to be effective and safe.
- To monitor for clinical response for appropriate continuation of therapy.

**Length of Authorization:**

- 6 months

**Requires PA:**

- Ivacaftor (Kalydeco®)
- Lumacaftor/ivacaftor (Orkambi®)
- Tezacaftor/ivacaftor (Symdeko®)
- Elexacaftor/Tezacaftor/ivacaftor (Trikafta™)

**Preferred Alternatives:**

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

**Table 1: Approved and Funded Indications for Oral Cystic Fibrosis Modulators**

Drug Name	FDA approved CFTR mutation	Age
<b>Ivacaftor (Kalydeco)</b>	E56K, G178R, S549R K1060T, G1244E, P67L, E193K, G551D, A1067T, S1251N R74W, L206W, G551S, G1069R, S1255P, D110E, R347H, D579G, R1070Q, D1270N, D110H, R352Q, S945L, R1070W G1349D, R117C, A455E, S977F, F1074L, R117H, S549N, F1052V, D1152H 3849 + 10kbC -T, 2789 +5G>A, 3272-26A-G, 711+3A-G, E831X, R117H	≥ 6 months
<b>Lumacaftor/ivacaftor (Orkambi)</b>	Homozygous Phe508del	≥ 2 years
<b>Tezacaftor/ivacaftor (Symdeko)</b>	Homozygous Phe508del, A455E, A1067T, D110E, D110H, D579G, D1152H, D1270N, E56K, E193K,	≥ 6 years

	E831X, F1052V, F1074L, K1060T, L206W, P67L, R74W, R1070W, R117C, R347H, R352Q, S945L, S977F, 711+3A→G, 2789+5G→A, 3272-26A→G, 3849+10kbC→T	
<b>Elexacaftor/tezacaftor/ivacaftor (Trikafta)</b>	At least Phe508del mutation (homozygous or heterozygous)	≥ 12 years

<b>Approval Criteria</b>		
1. Is this a request for continuation of therapy previously approved by the FFS program (patient already on ivacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor, or elexacaftor/tezacaftor/ivacaftor)?	<b>Yes:</b> Go to <b>Renewal Criteria</b>	<b>No:</b> Go to #2
2. Does the patient have a diagnosis of Cystic Fibrosis?	<b>Yes:</b> Record ICD10 code. Go to #3	<b>No:</b> Pass to RPh. Deny; medical appropriateness
3. Is the request from a practitioner at an accredited Cystic Fibrosis Center or a pulmonologist?	<b>Yes:</b> Go to #4	<b>No:</b> Pass to RPh. Deny; medical appropriateness
4. Is the request for an FDA approved age and CFTR gene mutation as defined in Table 1?	<b>Yes:</b> Go to #5	<b>No:</b> Pass to RPh. Deny; medical appropriateness  If unknown, there needs to be a CF mutation test to detect the presence of the CFTR mutation prior to use.
5. How many exacerbations and/or hospitalizations in the past 12 months has the patient had?	Prescriber must provide documentation before approval. Document baseline value. Go to #6	
6. Is the request for ivacaftor?	<b>Yes:</b> Go to #7	<b>No:</b> Go to #8

<b>Approval Criteria</b>		
7. Does the patient have a documented R117H mutation in the CFTR gene detected by a CF mutation test?	<b>Yes:</b> Pass to RPh. Refer request to Medical Director for manual review and assessment of clinical severity of disease for approval.	<b>No:</b> Go to #10  If unknown, there needs to be a CF mutation test to detect the presence of the CFTR mutation prior to use.  CF due to other CFTR gene mutations are not approved indications (including the F508del mutation).
8. Is the request for lumacaftor/ivacaftor?	<b>Yes:</b> Go to #9	<b>No:</b> Go to #10
9. Is the patient younger than 12 years of age?	<b>Yes:</b> Refer case to <u>OHP Medical Director</u> for manual review and assessment of clinical severity of disease	<b>No:</b> Go to #10
10. Is the patient on ALL the following drugs, or has had an adequate trial of each drug, unless contraindicated or not appropriate based on age <6 years and normal lung function? <ul style="list-style-type: none"> <li>• Dornase alfa; AND</li> <li>• Hypertonic saline; AND</li> <li>• Inhaled or oral antibiotics (if appropriate)?</li> </ul>	<b>Yes:</b> Go to #11	<b>No:</b> Pass to RPh. Deny; medical appropriateness
11. Is the patient on concomitant therapy with a strong CYP3A4 inducer (see Table 1)?	<b>Yes:</b> Pass to RPh. Deny; medical appropriateness	<b>No:</b> Go to #12

Approval Criteria		
12. What are the baseline liver function (AST/ALT) and bilirubin levels (within previous 3 months)?	Document labs. Go to #13 If unknown, these labs need to be collected prior to approval.	
13. Is medication dosed appropriately based on age, weight, and co-administered drugs (see dosing and administration below)?	<b>Yes:</b> Approve for 6 months.  If approved, a referral will be made to case management by the Oregon Health Authority.	<b>No:</b> Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there evidence of adherence and tolerance to therapy through pharmacy claims/refill history and provider assessment?	<b>Yes:</b> Go to #2	<b>No:</b> Pass to RPh; Deny (medical appropriateness)

## Renewal Criteria

<p>2. Does the patient have documented response to therapy as defined as below :</p> <p>For patients age <math>\geq 6</math> years:</p> <ul style="list-style-type: none"> <li>• An improvement or lack of decline in lung function as measured by the FEV1 when the patient is clinically stable; OR</li> <li>• A reduction in the incidence of pulmonary exacerbations; OR</li> <li>• A significant improvement in BMI by 10% from baseline?</li> </ul> <p>For patients age 2-5 years (cannot complete lung function tests)</p> <ul style="list-style-type: none"> <li>• Significant improvement in BMI by 10% from baseline; OR</li> <li>• Improvement in exacerbation frequency or severity; OR</li> <li>• Sweat chloride test has decreased from baseline by 20 mmol/L from baseline?</li> </ul>	<p><b>Yes:</b> Go to #3</p>	<p><b>No:</b> Pass to RPh. Deny; medical appropriateness</p>
<p>3. Have liver function tests been appropriately monitored? What are the most recent liver function tests (AST, ALT, and bilirubin)?</p> <p>Note: Monitoring LFTs is recommended every 3 months for the first year, followed by once a year.</p>	<p>Document. Go to #4</p> <p>Note: Therapy should be interrupted in patients with AST or ALT <math>&gt;5x</math> the upper limit of normal (ULN), or ALT or AST <math>&gt;3x</math> ULN with bilirubin <math>&gt;2x</math> ULN.</p>	
<p>4. Is the CFTR modulator dosed appropriately based on age, weight, and co-administered drugs (see dosing and administration below)?</p>	<p><b>Yes:</b> Approve for additional 12 months</p>	<p><b>No:</b> Pass to RPh. Deny; medical appropriateness</p>

## Dosage and Administration:

### Ivacaftor:

- Adults and pediatrics age  $\geq 6$  years: 150 mg orally every 12 hours with fat-containing foods
- Children age 6 months to  $< 6$  years:
  - 5 kg to  $< 7$  kg: 25 mg packet every 12 hours
  - 7 kg to  $< 14$  kg: 50 mg packet every 12 hours
  - $\geq 14$  kg: 75 mg packet every 12 hours
- Hepatic Impairment
  - Moderate Impairment (Child-Pugh class B):
    - Age  $\geq 6$  years: one 150 mg tablet once daily
    - Age 6 months to  $< 6$  years
      - with body weight  $< 14$  kg: 50 mg packet once daily
      - with body weight  $\geq 14$  kg : 75 mg packet of granules once daily
  - Severe impairment (Child-Pugh class C): Use with caution at a dose of 1 tablet or 1 packet of oral granules once daily or less frequently. For infants, children and adolescents: administer usual dose once daily or less frequently. Use with caution.
- Dose adjustment with concomitant medications:

Table 1. Examples of CYP3A4 inhibitors and inducers.

Drug co-administered with IVA	Co-administered drug category	Recommended dosage adjustment for IVA
Ketoconazole Itraconazole Posaconazole Voriconazole Clarithromycin Telithromycin	CYP3A4 strong inhibitors	Reduce IVA dose to 1 tablet or 1 packet of oral granules <b>twice weekly</b> (one-seventh of normal initial dose)
Fluconazole Erythromycin Clofazimine	CYP3A4 moderate inhibitors	Reduce IVA dose to 1 tablet or 1 packet of oral granules <b>once daily</b> (half of normal dose)

Rifampin Rifabutin Phenobarbital Phenytoin Carbamazepine St. John's wort	CYP3A4 strong inducers	Concurrent use is <b>NOT</b> recommended
Grapefruit Juice	CYP3A4 moderate inhibitors	

#### Lumacaftor/ivacaftor

- Adults and pediatrics age  $\geq 6$  years: 2 tablets (LUM 200 mg/IVA 125 mg) every 12 hours
- Pediatric patients age 6 through 11 years: 2 tablets (LUM 100mg/IVA 125 mg) every 12 hours
- Children age 2 to  $<6$  years:
  - $< 14$  kg: 1 packet (LUM 100mg/IVA125mg) every 12 hours
  - $\geq 14$  kg: 1 packet (LUM 150mg/IVA 188mg) every 12 hours
- Hepatic impairment
  - Moderate impairment (Child-Pugh class B):
    - Age  $\geq 6$  years: 2 tablets in the morning and 1 tablet in the evening
    - Age 2 to  $<6$  years: 1 packet in the morning and 1 packet every other day in the evening
  - Severe impairment (Child-Pugh class C): Use with caution after weighing the risks and benefits of treatment.
    - Age  $\geq 6$  years: 1 tablet twice daily, or less
    - Age 2 to  $<6$  years: 1 packet once daily, or less
- Dose adjustment with concomitant medications:
  - When initiating therapy in patients taking strong CYP3A inhibitors (see table above), reduce dose to 1 tablet daily for the first week of treatment. Following this period, continue with the recommended daily dose.

#### Tezacaftor/ivacaftor:

- Adults and pediatrics age  $\geq 6$  years weighing  $\geq 30$  kg : 1 tablet (TEZ 100 mg/IVA 150 mg) in the morning and IVA 150 mg in the evening
- Pediatrics age  $\geq 6$  years weighing  $< 30$  kg: TEZ 50mg/IVA 75 mg in the morning and IVA 75 mg in the evening
- Hepatic impairment
  - Moderate impairment (Child-Pugh class B):
    - 1 tablet (TEZ 100 mg/IVA 150 mg) in the morning. The evening IVA dose should not be administered.
  - Severe impairment (Child-Pugh class C):
    - 1 tablet (TEZ 100 mg/IVA 150 mg) in the morning (or less frequently). The evening IVA dose should not be administered.
- Dose adjustment with concomitant medications:

- When initiating therapy in patients taking moderate CYP3A inhibitors (see table above), reduce dose to:
  - On day 1, TEZ 100/IVA 150 once daily in the morning, and on day 2, IVA 150 mg once daily in the morning; continue this dosing schedule.
- When initiating therapy in patients taking strong CYP3A4 inhibitors (See table above), reduce dose to:
  - TEZ 100 mg/IVA 150 mg twice a week, administered 3 to 4 days apart. The evening dose of IVA 150 mg should not be administered.

Elexacaftor/tezacaftor/ivacaftor:

- Adults and pediatrics age ≥12 years: 2 tablets (ELX 100mg/TEZ 50 mg/IVA 75 mg) in the morning and IVA 150 mg in the evening
- Hepatic impairment
  - Moderate impairment (Child-Pugh class B): Use only if the benefits outweigh the risks.
    - 2 tablet (ELX 100 mg/TEZ 50 mg/IVA 75 mg) in the morning. The evening IVA dose should not be administered.
  - Severe impairment (Child-Pugh class C): Use not recommended
- Dose adjustment with concomitant medications:
  - Dosage adjustment for concomitant therapy with moderate CYP3A inhibitors (see table above):
    - 2 tablets (ELX 100 mg/ TEZ 50 mg/IVA 75 mg once daily in the morning, alternating with one IVA 150 mg tablet in the morning every other day.
  - Dosage adjustment for concomitant therapy with strong CYP3A4 inhibitors (See table above), reduce dose to:
    - 2 tablets (ELX 100 mg/TEZ 50 mg/IVA 75 mg twice a week, administered 3 to 4 days apart. The evening dose of IVA 150 mg should not be administered.

P&T Review: 6/20 (MH); (9/19); 9/18; 7/18; 11/16; 11/15; 7/15; 5/15; 5/14; 6/12  
 Implementation: TBD; 11/1/19; 11/1/2018; 1/1/16; 8/25/15; 8/12

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## Drug Class Update: Laxatives for Chronic Constipation

**Date of Review:** April 2020

**Date of Last Review:** July 2017

**Dates of Literature Search:** 1/1/2017 – 12/17/2019

### **Current Status of PDL Class:**

See **Appendix 1**.

### **Purpose for Class Update:**

The drugs for constipation class will be reviewed to determine if there is any relevant, updated evidence to be incorporated into the recommendations provided to the Oregon Health Plan (OHP). Evidence identified since the July 2017 review will be included.

### **Research Questions:**

- Is there evidence for differences in clinical efficacy or effectiveness for linaclotide, lubiprostone, alvimopan, methylnaltrexone, naloxegol, naldemedine, plecanatide, prucalopride, tegaserod, or tenapanor over traditional laxatives used to manage constipation?
- Is there evidence for differences in safety for linaclotide, lubiprostone, alvimopan, methylnaltrexone, naloxegol, naldemedine, plecanatide, prucalopride, tegaserod, or tenapanor over traditional laxatives used to manage constipation?
- Are there subgroups of patients based on demographics (e.g., age, racial or ethnic groups and gender), other medications, or co-morbidities for which one treatment for constipation is more effective or associated with fewer adverse events?

### **Conclusions:**

- Three systematic reviews<sup>1-3</sup> and 3 clinical guidelines<sup>4-6</sup> were published since the last laxative class update was presented to the P and T Committee.
- A 2018 Cochrane systematic review updated a 2012 publication which evaluated safety and efficacy of osmotic and stimulant laxatives in children with chronic idiopathic constipation (CIC).<sup>1</sup> The pooled analyses from 11 randomized controlled trials (RCT) suggest that polyethylene glycol (PEG) preparations may be superior to placebo, lactulose and milk of magnesia for childhood constipation.<sup>1</sup> However, the overall quality of the evidence for the primary outcome (number of stools per week) was low or very low due to sparse, heterogeneous data, and high risk of bias from the studies in the pooled analyses.<sup>1</sup> There is no evidence to demonstrate the superiority of lactulose in pediatric CIC when compared to the other agents studied.<sup>1</sup>
- A 2018 Cochrane update evaluated safety and efficacy for mu-opioid antagonists (MOAs) for alleviating opioid-induced constipation (OIC) in adults with cancer or receiving palliative care.<sup>2</sup> Moderate-quality evidence from one trial suggests naldemedine improves bowel function in patients with OIC and cancer in whom conventional laxatives have failed, but increases the risk of adverse events.<sup>2</sup> Moderate-quality evidence from 2 trials suggests methylnaltrexone improves bowel function in people receiving palliative care with OIC, and low-quality evidence shows that it does not increase adverse events.<sup>2</sup>

- A high-quality systematic review published in 2018 evaluated the efficacy of medications approved to treat OIC.<sup>3</sup> Twenty-six placebo-controlled RCTs evaluating methylnaltrexone, naloxone, naloxegol, alvimopan, prucalopride, lubiprostone, and naldemedine met inclusion criteria.<sup>3</sup> The most common primary outcome was 3 or more bowel movements (BMs) per week over the trial period.<sup>3</sup> In the meta-analysis, 51% of subjects who received an OIC treatment (MOAs, lubiprostone, or prucalopride) had a favorable response to therapy, compared with 33% of individuals randomized to placebo, for an overall number needed to treat (NNT) of 5.<sup>3</sup> The overall relative risk for failure to respond to therapy was significantly lower for those who received drug versus placebo [Relative Risk (RR) 0.70, 95% Confidence Interval (CI) 0.64 to 0.75].<sup>3</sup> Individually, the NNT for lubiprostone was 15, naloxegol was 7, methylnaltrexone and naloxone was 4, and naldemedine was 5.<sup>3</sup> Compared to other medications, lubiprostone was the least efficacious in treating OIC.<sup>3</sup> After pooling all treatments, adverse effects were significantly higher in those who received drug versus placebo, with a number needed to harm (NNH) of 20.<sup>3</sup> A limitation of this systematic review was the significant heterogeneity across 26 studies, likely owing to the inclusion of multiple drugs, varying baseline opioid use, and different subject populations (cancer versus non-cancer-related pain).<sup>3</sup>
- The 2018 American College of Gastroenterology (ACG) engaged a panel of gastroenterologists to update a 2014 monograph for treatment of irritable bowel syndrome (IBS).<sup>4</sup> Moderate-quality evidence suggests psyllium should be recommended as first-line therapy for overall symptom improvement in patients with IBS with constipation (IBS-C).<sup>4</sup> Strong recommendations based on moderate- to high-quality evidence suggest linaclotide, plecanatide, and lubiprostone improve symptoms among patients with IBS-C compared with placebo.<sup>4</sup>
- The 2019 Canadian Association of Gastroenterology (CAG) clinical practice guideline for management of IBS strongly recommended soluble fiber supplementation as an initial, low-cost, safe treatment option that is acceptable to patients and has moderate-quality evidence that it improves IBS-C symptoms.<sup>5</sup> High-quality evidence supports a strong recommendation for the use of linaclotide to improve IBS-C symptoms.<sup>5</sup> In light of the fact that lubiprostone treatment is expensive, and there are no comparative studies to evaluate whether it is more effective than other less expensive treatments, the consensus group made a conditional recommendation in favor of using lubiprostone in IBS-C patients based on moderate-quality evidence.<sup>5</sup> Plecanatide was not included in the CAG document because it is not commercially available in Canada.
- Recommendations of the American Gastroenterological Association (AGA) on the medical management of OIC were published in 2019.<sup>6</sup> Due to insufficient evidence, AGA does not recommend lubiprostone or prucalopride in patients with OIC. Strong recommendations based on moderate- to high-quality evidence are summarized below:
  - In patients with OIC, the AGA recommends use of laxatives as first-line agents (Quality of evidence: High).<sup>6</sup>
  - In patients with laxative refractory OIC, the AGA recommends naldemedine (Quality of evidence: High).<sup>6</sup>
  - In patients with laxative refractory OIC, the AGA recommends naloxegol (Quality of evidence: Moderate).<sup>6</sup>
- There is insufficient evidence that one drug is more effective or associated with fewer adverse events in specific subgroups of patients based on demographics (age, racial or ethnic groups and gender), other medications (e.g., opioids), or most co-morbidities.

#### **Recommendations:**

- Designate prucalopride, tegaserod, and tenapanor as non-preferred on the Practitioner-Managed Prescription Drug Plan (PMPDP) to assure use in OHP-funded conditions.
- Revise laxatives for constipation prior authorization (PA) criteria to include prucalopride, tegaserod, and tenapanor.
- Review drug costs in the executive session.

## Summary of Prior Reviews and Current Policy

Drugs for constipation were last reviewed by the P and T Committee at the July 2017 meeting when abbreviated drug reviews for plecanatide and naldemedine were presented. Constipation, IBS-C, and OIC are not currently funded under the Oregon Health Plan Prioritized List of Health Services.<sup>2</sup> Funding for drugs that treat constipation is dependent on whether constipation adversely affects, or is secondary to, an underlying medical condition covered by the prioritized list. Therefore, prior authorization criteria were implemented to help guide decision making for nonpreferred drug utilization in funded conditions. Nonpreferred drugs include: linaclotide, methylnaltrexone, naloxegol, naldemedine, alvimopan, lubiprostone, and plecanatide. Preferred laxatives on the PDL include: PEG, docusate, senna, magnesium hydroxide, calcium polycarbophil, bisacodyl, lactulose, psyllium, magnesium citrate, and methylcellulose. One hundred percent of OHP Fee-for-Service (FFS) utilization is for the preferred laxatives. Prior authorization criteria are included in **Appendix 3**.

## Background:

Functional bowel disorders are a spectrum of chronic gastrointestinal (GI) disorders characterized by predominant symptoms or signs of abdominal pain, bloating, distention, or bowel habit abnormalities (e.g., constipation, diarrhea, or mixed constipation and diarrhea).<sup>7</sup> These bowel disorders can be distinguished from other GI disorders based on chronicity (having symptoms for 6 months or greater at the time of presentation), current activity (symptoms present within the last 3 months), frequency (symptoms present, on average, at least 1 day per week), and the absence of obvious anatomic or physiologic abnormalities identified by routine diagnostic examinations.<sup>7</sup> Constipation can arise secondary to neurological conditions, such as Parkinson disease and multiple sclerosis; endocrine disorders, such as hypothyroidism and hypercalcemia; and prescribed medications, such as opiates or tricyclic antidepressants.<sup>8</sup> The functional bowel disorders are classified into 5 distinct categories: IBS, chronic idiopathic constipation (CIC), functional diarrhea, functional abdominal bloating/distention, and unspecified bowel disorder.<sup>7</sup> A sixth category, OIC, is distinct from the other bowel disorders because it has a specific etiology that can produce symptoms similar to CIC.<sup>7</sup>

Functional, idiopathic, constipation is a chronic disorder in which symptoms of difficult, infrequent, or incomplete defecation predominate.<sup>7</sup> Patients with CIC do not meet IBS criteria, although abdominal pain or bloating may be present but are not predominant symptoms.<sup>7</sup> In adults, the mean prevalence rate of CIC is approximately 14%.<sup>7</sup> Risk factors for CIC include female sex, reduced caloric intake, and increasing age.<sup>7</sup> The Rome III criteria<sup>9,10</sup> are used to define functional constipation by the presence of the following 3 conditions for at least 3 months:

- Insufficient criteria for irritable bowel syndrome
- Without the use of laxatives, loose stools are rarely present
- Presence of 2 or more of the following criteria:
  - straining during  $\geq 25\%$  of defecations
  - lumpy or hard stools during  $\geq 25\%$  of defecations
  - feeling of incomplete evacuation during  $\geq 25\%$  of defecations
  - feeling of anorectal obstruction or blockage during  $\geq 25\%$  of defecations
  - manually facilitating defecation during  $\geq 25\%$  of defecations
  - less than 3 unassisted bowel movements/week

Treatment of CIC should begin by educating the patient about constipation, eliminating medications (prescription, over-the-counter, complementary) that can cause or worsen constipation and asking the patient to maintain a diet that contains an adequate amount of fiber.<sup>7</sup> Insoluble, non-fermentable fiber accelerates intestinal transit by increasing stool biomass leading to direct stimulation of secretion and motility.<sup>7</sup> Constipated patients with severely delayed colon transit or

obstructed defecation are less likely to improve with fiber.<sup>7</sup> If a patient fails fiber therapy, laxative therapy can be initiated.<sup>7</sup> Laxatives either increase stool water content or accelerate bowel transit to alleviate constipation.<sup>8</sup> They are subdivided into 6 different categories depending on their mechanism of action:

- bulk-forming: calcium polycarbophil, methylcellulose, and psyllium
- lubricant: mineral oil
- stool softener: docusate
- stimulant: bisacodyl or senna
- osmotic: glycerin, lactulose, PEG, and sorbitol
- saline: magnesium hydroxide, magnesium citrate, and sodium phosphate

Irritable bowel syndrome is a disorder in which recurrent abdominal pain is associated with defecation or a change in bowel habits.<sup>7</sup> Disordered bowel habits are typically present (i.e., constipation, diarrhea, or a mix of constipation and diarrhea), as are symptoms of abdominal bloating or distention.<sup>7</sup> Symptom onset typically occurs at least 6 months before diagnosis and symptoms are present for at least 3 months. The world-wide prevalence of IBS is 11.2%.<sup>7</sup> Prevalence rates are higher for women than for men and younger people are more likely to be affected than those older than age 50 years.<sup>7</sup> Factors that trigger the onset or exacerbation of IBS symptoms include a prior gastroenteritis, food intolerances, chronic stress, diverticulitis, and surgery.<sup>7</sup> Therapeutic options to treat IBS-C include the prosecretory medications linaclotide and plecanatide. Linaclotide and plecanatide activate the cystic fibrosis transmembrane conductance regulator chloride channel by increasing luminal cyclic guanosine monophosphate.<sup>8</sup> Consequently, intestinal fluid is increased and intestinal transit is accelerated. An additional drug with Food and Drug Administration (FDA) approval for IBS-C is lubiprostone, a locally acting chloride channel activator that enhances intestinal fluid secretion and intestinal motility.

Tegaserod and prucalopride are 5-hydroxytryptamine-4 (5-HT<sub>4</sub>) receptor agonists which stimulate GI and colonic motility.<sup>8</sup> Tegaserod is FDA-approved for treatment of IBS-C and prucalopride is FDA approved for treatment of CIC. Tegaserod was withdrawn from the United States market in 2007 due to concerns involving possible cardiovascular adverse events. In 2019, tegaserod was re-introduced to the US market after FDA re-approval for use in IBS-C in women under 65 years of age. Prucalopride has been approved by the European Medicines Agency for the treatment of CIC in women since 2009. Prucalopride received FDA-approval in 2018 for treatment of CIC in adults. National Institute for Health and Care Excellence (NICE) guidance from 2010 recommends prucalopride as an option for the treatment of chronic constipation only in women for whom invasive treatment for constipation is being considered and after treatment failure with at least 2 laxatives from different classes, at the highest tolerated recommended doses for at least 6 months.<sup>11</sup>

Opioid-induced constipation has been defined by Rome IV criteria as a change from baseline bowel habits and defecation patterns after initiating opioid therapy, characterized by any of the following: reduced bowel frequency [less than 3 spontaneous bowel movements (SBMs) per week]; development or worsening of straining to pass a bowel movement; a sense of incomplete evacuation; or a patient's perception of distress related to bowel habits.<sup>7</sup> The occasional patient may also develop fecal impaction with overflow incontinence, while others may report symptoms compatible with overlapping opioid-induced bowel disorders (e.g., reflux, nausea, bloating).<sup>7</sup> In a systematic review of 8 placebo-controlled trials, the prevalence of OIC was 41% in patients with chronic non-cancer pain taking opioids.<sup>12</sup> In a study of cancer patients taking opioids for pain, the incidence of constipation was approximately 94%.<sup>13</sup> Three different classes of opioid receptors mediate the GI effects of opioid medications: kappa, delta and mu.<sup>6</sup> Opioids exert their GI effects via kappa-receptors in the stomach and small intestine and mu-receptors located in the small intestine and proximal colon.<sup>6</sup>

The initial treatment of OIC is similar to the treatment of CIC. Stimulant laxatives as monotherapy or in combination with a stool softener are initially recommended for both the prophylaxis and management of OIC in patients with cancer. Bulk-forming laxatives for not recommended for OIC due to the

increased risk of bowel obstruction. Peripheral-acting mu-opioid-receptor antagonists (i.e., methylnaltrexone, naloxegol, and naldemedine) are FDA-approved for the treatment of OIC in adults with non-cancer pain. These drugs block opioid receptors in the GI tract, antagonizing the constipating effects of opioids in the periphery without affecting analgesia. Another MOA, alvimopan, is only indicated for short-term use to prevent or decrease the course of postoperative ileus after bowel resection and is therefore available for hospital use only.<sup>12</sup> Lubiprostone is also FDA-approved for OIC in patients with chronic, non-cancer pain. A summary of GI drugs approved to treat CIC, IBS-C, and OIC for outpatient use is presented in **Table 1** (excluding laxatives).

**Table 1. Gastrointestinal Drugs FDA-Approved for Treatment of Constipation in an Outpatient Setting<sup>14,15</sup>**

Generic (Brand Name)	Indications	Dosing	Boxed Warning
<b>Guanylate Cyclase-C Agonists</b>			
Linaclotide (LINZESS)	CIC IBS-C	72- 145 mcg po once daily 290 mcg po once daily	Serious Dehydration in Pediatric Patients: Use is contraindicated in pediatric patients <6 years. Avoid use in pediatric patients 6 to 17 years of age.
Plecanatide (TRULANCE)	CIC IBS-C	3 mg po once a day 3 mg po once a day	Serious Dehydration in Pediatric Patients: Use is contraindicated in pediatric patients <6 years. Avoid use in pediatric patients 6 to 17 years of age.
<b>Chloride Channel Activator</b>			
Lubiprostone (AMITIZA)	CIC  IBS-C  OIC: chronic, non-cancer pain	24 mcg po twice daily  Females > 18 yo: 8 mcg po twice daily  24 mcg po twice daily	
<b>Peripherally Acting Mu-Opioid Antagonists</b>			
Naldemedine (SYMPROIC)	OIC: chronic, non-cancer pain	0.2 mg once daily	
Naloxegol (MOVANTIK)	OIC: chronic, non-cancer pain	25 mg once daily	
Methylnaltrexone (RELISTOR)	OIC with advanced illness (injection only)  OIC with chronic non-cancer pain (tablets and injection)	450 mg po once daily  12 mg SC once daily	
<b>Serotonin 5-HT(4) Receptor Agonists</b>			
Prucalopride (MOTEGRITY)	CIC	2 mg po once daily	
Tegaserod (ZELNORM)	IBS-C	Females < 65 yo: 6 mg po twice daily	
<b>Sodium/Hydrogen Exchanger</b>			
Tenapanor (IBSRELA)	IBS-C	50 mg po twice daily	Serious Dehydration in Pediatric Patients: Use is contraindicated in pediatric patients <12 years. Avoid use in pediatric patients 6 to 17 years of age.

Abbreviations: 5HT (4) = 5-hydroxytryptamine; CIC = chronic idiopathic constipation; IBS-C = irritable bowel syndrome with constipation; mcg = micrograms; mg = milligrams; OIC = opioid induced constipation; po = oral; SC = subcutaneous; yo = years old

Objective measures that assess the severity of constipation and its impact on quality of life may help providers decide on course of treatment or whether to pursue more diagnostic studies.<sup>16</sup> Although the Rome criteria are used to identify constipation and its subtypes, they do not assess severity of the condition.<sup>16</sup> Many measures have been developed to assess constipation specifically, with variable psychometric properties. These include the Constipation Assessment Scale, Constipation Scoring System, Patient Assessment of Constipation Symptom Questionnaire, Knowles-Eccersley-Scott Symptom Score, Garrigues Questionnaire, Chinese Constipation Questionnaire, and Constipation Severity Instrument.<sup>16</sup> Other measures assess all bowel function and incorporate measures of fecal incontinence or specifically address one aspect of constipation, such as obstructive defecation. The purpose of all of these measures is simply to develop a consistent means of categorizing the baseline severity of the disease and to follow response to treatment over time.<sup>16</sup>

### **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.

### **New Systematic Reviews:**

#### ***Cochrane: Osmotic and Stimulant Laxatives for the Management of Childhood Constipation***

A 2018 Cochrane systematic review updated a 2012 publication which evaluated safety and efficacy of osmotic (PEG, milk of magnesia, lactulose) and stimulant (cascara, senna, bisacodyl, mineral oil) laxatives in children aged 0 to 18 years with chronic constipation.<sup>1</sup> The literature search was conducted through March 2016. The primary outcome was frequency of defecation (number of stools per week). Secondary endpoints included fecal incontinence, disimpaction, need for additional therapies and adverse events.<sup>1</sup> Twenty-five RCTs (n=2310 participants) met inclusion criteria.<sup>1</sup> Fourteen studies were judged to be at high risk of bias due to lack of blinding, small population size, incomplete outcome data and selective reporting.<sup>1</sup>

A meta-analysis of two studies (n=101 patients) comparing PEG with placebo showed a significantly increased number of stools per week with PEG [mean difference (MD) 2.61 stools per week, 95% CI 1.15 to 4.08, I<sup>2</sup>=58%; low quality of evidence due to sparse data and inconsistency].<sup>1</sup> Common adverse events in the 2 studies included flatulence, abdominal pain, nausea, diarrhea and headache with no differences in incidence rates between the 2 groups.<sup>1</sup> Meta-analysis of 6 studies (n=465 participants) comparing PEG with lactulose showed more stools per week with PEG (MD 0.70, 95% CI 0.10 to 1.31, I<sup>2</sup>=69%), although follow-up was short (4 weeks); [low quality of evidence due to inconsistency and high risk of bias (lack of blinding and selective reporting)].<sup>1</sup> No serious adverse events were reported with either agent. Common adverse events in these studies included diarrhea, abdominal pain, nausea, vomiting and anal itching.<sup>1</sup> There was no statistically significant difference in the proportion of patients who experienced at least one adverse event; 37% of PEG patients experienced at least one adverse event compared to 45% of lactulose patients [RR 0.87, 95% CI 0.68 to 1.11; low quality of evidence due to sparse data (100 events)].<sup>1</sup> A meta-analysis of 3 studies with 211 participants compared PEG with milk of magnesia which showed PEG resulted in more stools per week (MD 0.69, 95% CI 0.48 to 0.89, I<sup>2</sup>=0%).<sup>1</sup> Overall, quality of the evidence was low due to sparse data and a high risk of bias (lack of blinding in one study and lack of blinding, incomplete outcome data and selective reporting in the other study).<sup>1</sup> No serious adverse events were reported.<sup>1</sup>

One study found a significant difference in number of stools per week favoring milk of magnesia over lactulose at 5 weeks [MD -1.51, 95% CI -2.63 to -0.39, 50 patients; low quality of evidence due to sparse data and a high risk of bias (lack of blinding and allocation concealment)].<sup>1</sup> A meta-analysis of 2 studies (n=287) comparing mineral oil with lactulose revealed a relatively large statistically significant difference in the number of stools per week favoring mineral oil [MD 4.94, 95% CI 4.28 to 5.61, I<sup>2</sup>=0%; low quality of evidence due to sparse data and high risk of bias (lack of blinding in both studies)].<sup>1</sup> No serious adverse events were reported.<sup>1</sup> No statistically significant differences in the number of stools per week were found between dietary fiber mix and lactulose (1 study, 125 patients), senna and lactulose (1 study, 21 patients), PEG and dietary fiber (1 study, 83 patients; MD 0.20, 95% CI -0.64 to 1.04), and PEG and mineral oil (2 studies, 261 patients; MD 0.35, 95% CI -0.24 to 0.95).<sup>1</sup>

In summary, the pooled analyses from 11 RCTs suggest that PEG may be superior to placebo, lactulose and milk of magnesia for childhood constipation.<sup>1</sup> However, the overall quality of the evidence for the primary outcome (number of stools per week) was low or very low due to sparse, heterogeneous data, short follow-up and high risk of bias in the studies.<sup>1</sup> Low quality evidence also suggests mineral oil may be efficacious.<sup>1</sup> There is no evidence to assess efficacy of lactulose relative to other agents and there is a lack of placebo-controlled studies.<sup>1</sup> Further research is needed to investigate the relative efficacy of these agents for childhood constipation.<sup>1</sup>

#### ***Cochrane: Mu-Opioid Antagonists in Opioid Induced Constipation in Adults with Cancer or Receiving Palliative Care***

A 2018 Cochrane update evaluated safety and efficacy of MOAs for alleviating OIC in adults with cancer or receiving palliative care.<sup>2</sup> The trials evaluated oral naldemedine and naloxone, and subcutaneous methylnaltrexone.<sup>2</sup> The literature search was completed through August 2017. Four new trials were identified for this update, bringing the total number included in the review to eight trials involving 1022 adults. All trials were vulnerable to biases; four were at a high risk of bias as they involved a sample of fewer than 50 participants per arm.<sup>2</sup> All 8 trials had unclear risk of selection bias as they under-reported allocation concealment or random sequence generation (or both), and 7 trials were at an unclear risk of reporting bias as they did not provide a protocol.<sup>2</sup> The primary efficacy outcome was bowel movement (BM) in the first 24 hours and between days 1 and 14 after the first dose.<sup>2</sup> Secondary outcomes included number of subjects who dropped out due to adverse effects, bowel transit time, relief of abdominal pain, and use of rescue medication for BM.

One trial (n=225) compared 3 doses of naldemedine (0.1 mg, 0.2 mg, or 0.4 mg) once daily to placebo in patients with cancer when conventional laxatives had failed. Overall, there were more spontaneous BM over the 2-week treatment period for the naldemedine group (RR 1.93, 95% CI 1.36 to 2.74, NNT=3; moderate-quality evidence).<sup>2</sup> Lower doses resulted in fewer spontaneous BMs than higher doses (0.1 mg vs. 0.2 mg: RR 0.73, 95% CI 0.55 to 0.95; 0.1 mg vs. 0.4 mg: RR 0.69, 95%CI 0.53 to 0.89; moderate-quality evidence).<sup>2</sup> The proportion of participants who had a rescue-free BM over the 2 weeks differed by dose of naldemedine, with the higher dose resulting in more BMs (0.1 mg: 56.4%; 0.2 mg: 77.6%; 0.4 mg: 82.1%; moderate-quality evidence).<sup>2</sup> There was moderate-quality evidence that naldemedine had no effect on opiate withdrawal over 2 weeks (0.1 mg: MD -0.13, 95% CI -0.57 to 0.31; 0.2 mg: MD -0.40, 95% -0.87 to 0.07; 0.4 mg: MD -0.02, 95% CI -0.45 to 0.41).<sup>2</sup> There were 5 serious adverse events with naldemedine but it was not clear if the any of the events were medication-related (low-quality evidence).<sup>2</sup> There was a higher incidence of non-serious adverse events (abdominal pain, nausea, and vomiting) in the naldemedine groups compared to placebo (RR 1.36, 95% CI 1.04 to 1.79, moderate-quality evidence).<sup>2</sup> The most common adverse event was diarrhea, but there was no difference in the proportion of patients impacted in either arm (RR 1.58, 95% CI 0.97 to 2.57, moderate-quality evidence).<sup>2</sup>

Two trials (n=287) compared methylnaltrexone to placebo in palliative care patients with OIC in which conventional laxatives had failed.<sup>2</sup> In the combined analysis, methylnaltrexone induced more BMs within 24 hours of the first dose compared to placebo (RR 2.77, 95% CI 1.91 to 4.04, I<sup>2</sup>=0%; moderate-quality evidence).<sup>2</sup> In the combined analysis, methylnaltrexone induced more BMs over 2 weeks (RR 9.98, 95% CI 4.96 to 20.09, I<sup>2</sup>=0%; moderate-quality evidence).<sup>2</sup>

proportion of participants who had a rescue-free BM response within 24 hours of the first dose was 59.1% in the methylnaltrexone arm and 19.5% in the placebo arm.<sup>2</sup> There was moderate-quality evidence that the rate of opioid withdrawal was not affected.<sup>2</sup> There was no difference in the proportion of participants who experienced an adverse event between methylnaltrexone and placebo (RR 1.17, 95% CI 0.94 to 1.45;  $I^2=74%$ ; low-quality evidence).<sup>2</sup> However, methylnaltrexone increased the likelihood of abdominal pain and flatulence compared to placebo (RR 2.39, 95% CI 1.07 to 5.34 and RR 2.09, 95% CI 1.07 to 4.08 respectively; low-quality evidence).<sup>2</sup>

In summary, there is moderate-quality evidence from one trial that suggested naldemedine improves bowel function in OIC for patients with cancer in whom conventional laxatives had failed, but at the increased risk of adverse events.<sup>2</sup> There is moderate-quality evidence from 2 trials that methylnaltrexone improves bowel function in people receiving palliative care with OIC and low-quality evidence that it does not increase adverse events.<sup>2</sup> There is insufficient evidence to assess the efficacy of naloxone as OIC trials with naloxone did not assess laxation.<sup>2</sup>

### ***Efficacy of Treatments for Opioid-Induced Constipation***

A high quality systematic review published in 2018 updated a previously published meta-analysis that evaluated the efficacy of medications approved to treat OIC.<sup>3</sup> The literature search included evidence published through March 2017. Twenty-six placebo-controlled RCTs evaluating methylnaltrexone, naloxone, naloxegol, alvimopan, prucalopride, lubiprostone, and naldemedine met inclusion criteria.<sup>3</sup> Over 9000 patients were enrolled in these trials. Baseline narcotic daily doses ranged from morphine equivalents of 20 to 2000 mg.<sup>3</sup> Opioid types varied from oxycodone to morphine to methadone.<sup>3</sup> Most of the RCTs provided moderate to high quality evidence.<sup>3</sup> Concerns about randomization, allocation concealment, and blinding in some of the studies resulted in a downgrade of quality assessment.<sup>3</sup> Two definitions of OIC were accepted including constipation associated with initiation of opioids, and fewer than 3 SBMs per week with at least one symptom of constipation (e.g., hard stools, sensation of incomplete evacuation, or moderate to severe straining in 25% of bowel movements after initiation of opioids).<sup>3</sup> The primary outcome was defined as treatment failure compared with placebo.<sup>3</sup> The most common primary outcome was 3 or more complete SBMs a week over the trial period.<sup>3</sup> Secondary efficacy outcomes included overall adverse events as well as individual rates of diarrhea, abdominal pain, nausea, and vomiting.<sup>3</sup>

A total of 1619 patients participated in the 6 methylnaltrexone trials. Patients received dosages of methylnaltrexone ranging from 12 mg to 450 mg, over 0.5 to 4 weeks in duration.<sup>3</sup> Of the 1004 individuals who received methylnaltrexone, 48% failed to respond (response defined as  $\geq 3$  BMs per week) compared with 72% of who received placebo.<sup>3</sup> Methylnaltrexone was more efficacious than placebo but there was significant heterogeneity between studies (RR, 0.62; 95% CI, 0.49 to 0.78;  $P<0.001$ ;  $I^2=77.2$ ; moderate quality evidence).<sup>3</sup> Five trials ( $n=482$ ) examined the use of naloxone in doses ranging from 2 to 40 mg once daily versus placebo over 3 to 12 week in patients with OIC. Of note, naloxone is not currently FDA-approved for use in OIC. A total of 44% of patients failed to respond to naloxone compared to 70% of patients on placebo (RR, 0.63;  $P<0.001$ ; 95% CI not reported;  $I^2=0.0%$ ; moderate-quality evidence).<sup>3</sup>

Four trials examined the efficacy of alvimopan compared with placebo in OIC. Overall, 433 of 1060 (40.8%) patients receiving alvimopan failed to respond compared with 280 of 519 (53.9%) patients on placebo.<sup>3</sup> Three trials evaluated dosages of 0.5 and 1 mg daily, but the fourth trial used both a 1- and 2-mg total daily dosage.<sup>3</sup> Alvimopan was more efficacious than placebo (RR 0.68;  $P<0.001$ , 95% CI not reported), with some heterogeneity between trials ( $I^2=56.3%$ ).<sup>3</sup> Four RCTs compared naldemedine to placebo in OIC. Overall, 45% of patients on naldemedine failed to respond compared with 65% patients who received placebo (RR, 0.65;  $P<0.001$ ; 95% CI not reported; moderate quality evidence) but there was significant heterogeneity across trials ( $I^2=79.6%$ ).<sup>3</sup>

Three trials ( $n=1522$ ) compared naloxegol with placebo.<sup>3</sup> Moderate quality evidence showed that 58% of patients who received naloxegol failed to respond, compared with 71% of patients who received placebo (RR, 0.77; 95% CI, 0.61 to 0.97;  $P=0.026$ ).<sup>3</sup> The 2 trials that compared the 12.5- and 25-mg doses (the 2

doses currently approved by the FDA) did not find a significant difference in efficacy between doses (RR 1.11; 95% CI, 0.94–1.30; P=0.208).<sup>3</sup> There was significant heterogeneity among the 3 trials (I<sup>2</sup>=86.4%).<sup>3</sup>

Lubiprostone was compared to placebo in 3 RCTs (n=1284).<sup>3</sup> Moderate quality evidence showed 62% of patients who received lubiprostone failed to respond compared with 69% of patients who received placebo (RR, 0.90; 95% CI, 0.83 to 0.97; P=0.005; I<sup>2</sup>=0%).<sup>3</sup> Only one placebo-controlled, double-blind trial compared prucalopride with placebo.<sup>3</sup> This trial showed modest results in favor of prucalopride compared to placebo in treating OIC (RR, 0.88; 95% CI, 0.68 to 0.98; P=0.032).<sup>3</sup>

Twenty-three placebo-controlled RCTs provided data regarding adverse events experienced within each group. In these trials, 58% of participants given a drug experienced at least one new-onset adverse event, compared with 53% of those given placebo.<sup>3</sup> This difference was significant (incidence rate ratio, 1.10; 95% CI, 1.05 to 1.16; P<0.001), with an overall NNH of 21 and no significant heterogeneity across trials (I<sup>2</sup>=0.0%).<sup>3</sup> The 3 most common adverse effects were diarrhea (8.5%), abdominal pain (12.8%), and nausea/vomiting (11.5%).<sup>3</sup> Participants who received a study drug were significantly more likely to experience all 3 adverse events compared with placebo (P=0.009, 95% CI not reported).<sup>3</sup> The overall drop-out rate owing to adverse events (only 20 studies reported these data) were 7.4% and 4.7% for drug and placebo, respectively (P=0.002, 95% CI not reported), resulting in an NNH of 36 (95% CI, 22 to 96).<sup>3</sup>

In summary, 51% of subjects who received an OIC treatment (MOAs, lubiprostone, or prucalopride) responded to therapy, compared with 33% of individuals randomized to placebo, for an overall NNT of 5 (95% CI, 4 to 7).<sup>3</sup> The overall relative risk for failure to respond to therapy was significantly lower for those who received drug rather than placebo treatment (RR, 0.70; 95% CI, 0.64 to 0.75).<sup>3</sup> Individually, the NNTs for lubiprostone, naloxegol, methylnaltrexone, naloxone, and naldemedine were as follows: 15 (95% CI, 9 to 51), 7 (95% CI, 4 to 6), 4 (95% CI, 3 to 6), 4 (95% CI, 4 to 6), and 5 (95% CI, 4 to 8), respectively.<sup>3</sup> Compared to other agents, lubiprostone had the least efficacy in treating OIC based on failure to respond to therapy. After pooled analysis of all treatments for OIC, adverse effects were significantly higher in those who received active drug compared with placebo, with a NNH of 20.<sup>3</sup> A limitation of this systematic review was the significant heterogeneity across 26 studies, likely owing to the inclusion of multiple agents, varying baseline opioid use, and different subject populations (cancer versus non-cancer-related pain).<sup>3</sup>

After review, 7 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses or failure to meet AMSTAR criteria),<sup>17-24</sup> 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:**

#### ***2018 American College of Gastroenterology: Management of Irritable Bowel Syndrome***

The American College of Gastroenterology (ACG) coordinated a high quality systematic review to assess the efficacy of pharmacologic therapies in treatment of IBS.<sup>4</sup> Parallel-group RCTs that compared pharmacologic agents with placebo in adults over 16 years of age were included in the review. The literature search was completed in July 2017. Outcome measures included global assessment of IBS cure or improvement, abdominal pain cure or improvement, and global IBS symptom or abdominal pain scores. An unrestricted educational grant was provided to the ACG Institute for Clinical Research and Education from Allergan and Ironwood Pharmaceuticals.<sup>4</sup> In addition, several authors served as consultants or speakers for various manufacturers. The systematic review was drafted before funding was obtained.<sup>4</sup> Strong recommendations with moderate- to high-quality evidence are summarized below.

1. Fiber is recommended for overall symptom improvement in IBS patients (Recommendation: strong; Quality of evidence: moderate).<sup>4</sup> Psyllium, but not wheat bran, is recommended for overall symptom improvement in IBS patients (Recommendation: strong; Quality of evidence: moderate).<sup>4</sup> Poorly fermentable, soluble fiber remains an evidence-based treatment for IBS.<sup>4</sup> Insoluble fiber may exacerbate pain and bloating in IBS, and has no evidence for efficacy.<sup>4</sup> The low cost and lack of significant adverse effects makes soluble fiber a reasonable first-line therapy for IBS patients and, in combination with the moderate quality of evidence, is the basis of a strong recommendation.<sup>4</sup>

2. Linaclotide is recommended for overall symptom improvement in IBS-C patients (Recommendation: strong; Quality of evidence: high).<sup>4</sup> Four placebo-controlled RCTs at low risk of bias were identified (n=2867 patients).<sup>4</sup> Meta-analysis of the results from the 4 RCTs favored linaclotide over placebo for improvement of IBS symptoms (RR=0.81; 95% CI 0.77 to 0.85; NNT=6; I<sup>2</sup>=0%).<sup>4</sup> All 4 trials reported on abdominal pain improvement as an endpoint, and linaclotide was favored over placebo (RR=0.82; 95% CI 0.75 to 0.89; NNT=8).<sup>4</sup> Adverse events were reported in 3 trials, and were more frequent in the linaclotide arm compared to placebo (RR=1.10; 95% CI 1.01 to 1.19).<sup>4</sup> Diarrhea occurred more frequently in the linaclotide arm compared to placebo (RR=6.81; 95% CI 4.69 to 9.90; NNH=7).<sup>4</sup>

3. Plecanatide is recommended for overall symptom improvement in IBS-C patients (Recommendation: strong; Quality of evidence: moderate).<sup>4</sup> Three RCTs (n=2612) were identified, 2 phase 3 RCTs published in press in a single article, and 1 dose ranging trial published in abstract form only.<sup>4</sup> The phase 3 RCTs had a low risk of bias.<sup>4</sup> Pooled data from the 2 RCTs suggests a positive effect of plecanatide on improving IBS symptoms compared to placebo (RR=0.88; 95% CI 0.84 to 0.92; NNT=10; I<sup>2</sup>=0%).<sup>4</sup> Total adverse events data were not available for the 3 studies individually, but were pooled for the 2 RCTs.<sup>4</sup> Twenty-four percent of patients assigned to 3 mg once daily of plecanatide reported any adverse event, compared with 20% of those randomized to 6 mg once daily of plecanatide, and 19% of those allocated to placebo.<sup>4</sup> Rates of diarrhea were higher with plecanatide versus placebo (RR=4.22; 95% CI 1.29 to 13.76; NNH=33).<sup>4</sup>

4. Lubiprostone is recommended for overall symptom improvement in IBS-C patients (Recommendation: strong; Quality of evidence: moderate).<sup>4</sup> Three trials at low risk of bias were identified.<sup>4</sup> In a meta-analysis, lubiprostone was more effective than placebo in improving IBS symptoms (RR=0.91; 95% CI 0.87 to 0.95; NNT=13, I<sup>2</sup>=0%).<sup>4</sup> Adverse events were reported by 66% of patients receiving lubiprostone compared with 58% of patients on placebo (RR=1.13; 95% CI 0.87 to 1.48).<sup>4</sup> The only symptom to occur more frequently with lubiprostone was diarrhea (NNH=10).<sup>4</sup> Only 1 trial reported the incidence of nausea but there was no significant difference in rates between lubiprostone and placebo.<sup>4</sup> This recommendation differs from the Canadian guideline, as CAG made a conditional recommendation to recommend use of lubiprostone in IBS-C due to insufficient comparative evidence and the high cost of lubiprostone.<sup>5</sup>

### **Canadian Association of Gastroenterology Clinical Practice Guideline for the Management of Irritable Bowel Syndrome**

The CAG clinical practice guideline for management of IBS was based on a literature search conducted through March 2017.<sup>5</sup> The systematic review used by the ACG in 2014 was updated with new evidence to guide development of the guideline.<sup>25</sup> The consensus group was a diverse group of practitioners and included a patient representative. Written disclosures of any potential conflicts of interest for the 24 months before the consensus meeting were provided by all participants and made available to all group members.<sup>5</sup> Funding for the consensus group meeting was provided by unrestricted grants to the CAG by Allergan Canada Inc. and Proctor & Gamble Canada.<sup>5</sup> The CAG administered all aspects of the meeting, and the funding sources had no involvement in the process of drafting and approval of these guidelines.<sup>5</sup> Several authors reported participating on advisory boards or speaker's bureaus for various pharmaceutical manufacturers. Recommendations with moderate to high quality evidence are summarized below. Plecanatide was not evaluated because it is not commercially available in Canada.

1. Psyllium supplementation is recommended to improve IBS-C symptoms (Recommendation: Strong; Quality of evidence: Moderate).<sup>5</sup> For this recommendation, a prior systematic review and meta-analysis was updated with one additional RCT for a total of 15 RCTs (n=946).<sup>5</sup> Risk of bias was unclear in the majority of studies.<sup>5</sup> Overall, fiber supplementation was favored over placebo or no treatment (RR of IBS not improving 0.87; 95% CI, 0.80 to 0.94; P=0.0003).<sup>5</sup> In the updated meta-analysis (7 studies, n=606), there was no increase in overall adverse events with fiber compared with placebo (36.6% vs. 25.1%; RR 1.06; 95% CI 0.92 to 1.22).<sup>5</sup> There were insufficient data from individual studies to assess adverse events according to fiber type.<sup>5</sup> Based on the evidence for efficacy and safety, the consensus group strongly recommended soluble fiber supplementation as a low-cost, safe treatment option that is acceptable to patients and has moderate-quality evidence that it improves IBS symptoms.<sup>5</sup>

2. Lubiprostone is recommended to improve IBS symptoms (Recommendation: Conditional; Quality of evidence: Moderate). Evidence for lubiprostone is available from 3 RCTs in IBS-C patients (n=1366).<sup>5</sup> All 3 of the trials used Rome criteria to define IBS-C, and all were at low risk of bias.<sup>5</sup> One trial was a dose-range, phase 2 study that assessed lubiprostone 8–24 mcg twice daily, and two trials were phase 3 studies evaluating 8 mcg twice daily.<sup>5</sup> In the pooled analysis, lubiprostone was more effective than placebo (RR of IBS not improving 0.91; 95% CI 0.87–0.95; P<0.0001; NNT 12.4; 95% CI 8-25).<sup>5</sup> In the phase 2 study, there was moderate-quality evidence that lubiprostone improved overall IBS symptoms, but the effect on abdominal pain was only statistically significant for the first 2 months, but not the third month, of treatment.<sup>5</sup> No comparative studies have evaluated whether lubiprostone is more effective than other much less expensive treatment options, so the consensus group made a conditional recommendation in favor of lubiprostone in IBS-C patients.<sup>5</sup>

3. Linaclotide is recommended to improve IBS-C symptoms (Recommendation: Strong; Quality of evidence: High). For this recommendation, a prior systematic review and meta-analysis was updated with one additional RCT (n=172), for a total of 4 RCTs (n=2867).<sup>5</sup> All trials used Rome criteria to define IBS-C, and all were at low risk of bias.<sup>5</sup> In the pooled analysis, linaclotide was more effective than placebo (RR of IBS not improving 0.81; 95% CI 0.77 to 0.85; P<0.00001; NNT 6; 95% CI, 5 to 8).<sup>5</sup> Linaclotide also improved abdominal pain compared with placebo (RR for no improvement 0.82; 95% CI 0.75 to 0.89; P<0.001; NNT 8).<sup>5</sup> Adverse event data were available from 3 RCTs. The pooled incidence of any adverse event was significantly greater among patients who received linaclotide versus those who received placebo (49.6% vs. 45.2%; RR 1.10; 95% CI 1.01 to 1.19; NNH 12).<sup>5</sup> Linaclotide was associated with higher rates of diarrhea (4 studies; RR 6.81; 95% CI 4.69 to 9.90; NNH 7) and flatulence (2 studies; RR 2.27; 95% CI 1.18–4.36; NNH 50) compared with placebo.<sup>5</sup>

### 2019 American Gastroenterological Association: Medical Management of Opioid-Induced Constipation

The official recommendations of the American Gastroenterological Association (AGA) on the medical management of OIC were published in 2019. The guideline was developed by the AGA Institute’s Clinical Guidelines Committee and approved by the AGA Governing Board. It is accompanied by a technical review that is a compilation of clinical evidence from which these recommendations were formulated.<sup>6</sup> Development of this guideline and its accompanying technical review was fully funded by the AGA Institute with no additional outside funding.<sup>6</sup> Recommendations are summarized in **Table 2**.

**Table 2. Summary of Recommendations of the AGA Clinical Guidelines for the Medical Management of Opioid-Induced Constipation<sup>6</sup>**

Recommendation	Strength of Recommendation	Quality of Evidence
<b>Traditional Laxatives</b>		
Laxatives recommended as first-line agents	Strong	Moderate
<b>Opioid Receptor Antagonists</b>		
Naldemedine recommended for laxative refractory OIC	Strong	High
Naloxegol recommended for laxative refractory OIC	Strong	Moderate

Methylalntrexone recommended for refractory OIC	Conditional	Low
<b>Chloride Channel Activator</b>		
Insufficient evidence to recommend lubiprostone	No Recommendation	Evidence Gap
<b>Selective 5-HT (4) Agonist</b>		
Insufficient evidence to recommend prucalopride	No Recommendation	Evidence Gap

#### New Formulations or Indications:

1. Prucalopride (Motegrity™) tablets received FDA approval in December 2018. Prucalopride is a 5-HT<sub>4</sub> agonist indicated for the treatment of CIC in adults.<sup>26</sup> The recommended dose is 2 mg orally, once daily in adults with normal renal function.<sup>26</sup> For patients with severe renal impairment (creatinine clearance less than 30 mL/min) the dose should be reduced to 1 mg once daily.<sup>26</sup> The most common adverse reactions (≥2%) are headache, abdominal pain, nausea, diarrhea, abdominal distension, dizziness, vomiting, flatulence, and fatigue.<sup>26</sup> Patients should be monitored for persistent worsening of depression and emergence of suicidal thoughts and behavior while taking prucalopride.<sup>26</sup> The drug should be discontinued if their depression is persistently worse or they experience emerging suicidal thoughts.

2. Tegaserod (Zelnorm™) was previously indicated for all women with IBS-C. Tegaserod was withdrawn from the United States market in 2007 due to concerns involving possible cardiovascular adverse events. In 2019, tegaserod was re-introduced to the US market after FDA re-approval for use in IBS-C in women under 65 years of age.<sup>27</sup> The safety and efficacy of tegaserod has not been established in men with IBS-C.<sup>27</sup> The recommended dose is 6 mg orally taken twice daily on an empty stomach. If patients have not an adequate response to tegaserod after 4 to 6 weeks of treatment, the drug should be discontinued.<sup>27</sup>

3. Tenapanor (Ibsrela®) tablets received FDA approval September 2019. Tenapanor is a sodium/hydrogen exchanger-3 (NHE3) inhibitor approved for the treatment of IBS-C in adults.<sup>28</sup> The recommended dose is 50 mg orally twice daily on an empty stomach.<sup>28</sup> The drug is contraindicated in pediatric patients less than 6 years of age or patients with a known or suspected mechanical GI obstruction.<sup>28</sup> The most serious adverse effects reported greater than or equal to 2% include severe diarrhea, abdominal distension, flatulence, and dizziness.<sup>28</sup>

4. Lactitol (Pizensy®) oral solution received FDA approval February 2020. Lactitol is an osmotic laxative indicated for the treatment of CIC in adults.<sup>29</sup> The approval is based on an 594-patient, six-month, randomized, placebo-controlled trial.<sup>29</sup> Most of the subjects enrolled in this trial were women (76%).<sup>29</sup>

The efficacy of lactitol was assessed using a responder analysis and change-from-baseline in the complete spontaneous bowel movements endpoint, using information provided by patients after each bowel movement in an electronic diary.<sup>29</sup> The primary efficacy analysis was based on the first 12 weeks of the 6-month treatment period for 594 patients.<sup>29</sup> A responder was defined as a patient who had at least 3 BMs in a given week and an increase of at least 1 BM from baseline in the same week for at least 9 weeks out of the first 12 weeks of treatment and at least 1 BM in at least 3 of the last 4 weeks of the treatment period.<sup>29</sup> Twenty-five percent of patients randomized to lactitol (n=291) responded to therapy compared with 13% of patients (n=303) in the placebo group (treatment difference: 12%, 95% CI 6.0 to 18.5, p <0.05).<sup>29</sup>

In clinical testing, the most common adverse reactions were upper respiratory tract infections, flatulence, diarrhea, increased blood creatinine phosphokinase, abdominal distension, and increased blood pressure.<sup>29</sup>

**New FDA Safety Alerts:**

**Table 3. Description of new FDA Safety Alerts**

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Tegaserod <sup>27</sup>	Zelnorm®	3/19	Contraindications, Warnings and Precautions	<p><b>Contraindications:</b> Package label revised to include additional contraindications in patients with myocardial infarction (MI), stroke, transient ischemic attack (TIA), or angina. In addition, a history of colitis or other forms of intestinal ischemia were added as contraindications.</p> <p><b>Warnings and Precautions:</b> 2 additional warnings and precautions were added to the tegaserod label.</p> <p>1. Cardiovascular Ischemic Events: Stroke, MI, and cardiovascular death (major adverse cardiovascular events [MACE]) have been reported in adults taking tegaserod who had an increased risk of developing an adverse cardiovascular event based on their medical history. Tegaserod is contraindicated in patients with a history of MI, stroke, TIA, or angina. Assess female patients less than 65 years of age for a history of cardiovascular disease and cardiovascular risk factors prior to treatment with tegaserod.<sup>27</sup></p> <p>2. Suicidal Ideation and Behavior: Suicide, suicidal attempt and ideation, and self-injurious behavior have been reported in clinical trials of IBS-C and other gastrointestinal motility disorders. The frequency of suicidal ideation or attempts with tegaserod treatment (8 patients out of 10,003) was higher than placebo (1 patient out of 5,425). Suicidal ideation/behavior in clinical trials was proportionately more frequent among patients receiving antidepressant medication.<sup>27</sup> Monitor all tegaserod-treated patients for clinical worsening of depression and emergence of suicidal thoughts and behaviors, especially during the initial few months of treatment. Counsel family members and caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Instruct patients to immediately discontinue tegaserod and contact their healthcare provider if their depression is persistently worse or they are experiencing emergent suicidal thoughts or behaviors.<sup>27</sup></p>

**Randomized Controlled Trials:**

A total of 71 citations were manually reviewed from the initial literature search. After further review, 71 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).

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29. Pizensy®(lactitol) Oral Solution Prescribing Information. Braintree, MA; Braintree Laboratories, Inc. February 2020.

**Appendix 1: Current Preferred Drug List**

<u>Generic</u>	<u>Brand</u>	<u>Form</u>	<u>Route</u>	<u>PDL</u>
bisacodyl	LAXATIVE	TABLET	ORAL	Y
bisacodyl	LAXATIVE FEMININE	TABLET	ORAL	Y
bisacodyl	WOMEN'S LAXATIVE	TABLET	ORAL	Y
bisacodyl	BISACODYL	TABLET DR	ORAL	Y
bisacodyl	BISA-LAX	TABLET DR	ORAL	Y
bisacodyl	DUCODYL	TABLET DR	ORAL	Y
bisacodyl	GENTLE LAXATIVE	TABLET DR	ORAL	Y
bisacodyl	LAXATIVE	TABLET DR	ORAL	Y
bisacodyl	MODANE	TABLET DR	ORAL	Y
bisacodyl	WOMEN'S GENTLE LAXATIVE	TABLET DR	ORAL	Y
bisacodyl	WOMEN'S LAXATIVE	TABLET DR	ORAL	Y
calcium polycarbophil	FIBER	TABLET	ORAL	Y
calcium polycarbophil	FIBER LAXATIVE	TABLET	ORAL	Y
calcium polycarbophil	FIBER TABS	TABLET	ORAL	Y
calcium polycarbophil	FIBER-LAX	TABLET	ORAL	Y
calcium polycarbophil	KONSYL FIBER	TABLET	ORAL	Y
cellulose	UNIFIBER	POWDER	ORAL	Y
docusate calcium	DOCUSATE CALCIUM	CAPSULE	ORAL	Y
docusate calcium	KAOPECTATE	CAPSULE	ORAL	Y
docusate calcium	KAO-TIN	CAPSULE	ORAL	Y
docusate calcium	STOOL SOFTENER	CAPSULE	ORAL	Y
docusate sodium	COLACE	CAPSULE	ORAL	Y
docusate sodium	COLACE CLEAR	CAPSULE	ORAL	Y
docusate sodium	DOC-Q-LACE	CAPSULE	ORAL	Y
docusate sodium	DOCUSATE SODIUM	CAPSULE	ORAL	Y
docusate sodium	DOCUSIL	CAPSULE	ORAL	Y
docusate sodium	DOK	CAPSULE	ORAL	Y
docusate sodium	SOF-LAX	CAPSULE	ORAL	Y
docusate sodium	STOOL SOFTENER	CAPSULE	ORAL	Y
docusate sodium	DOCU LIQUID	LIQUID	ORAL	Y
docusate sodium	DOCUSATE SODIUM	LIQUID	ORAL	Y
docusate sodium	SILACE	LIQUID	ORAL	Y
docusate sodium	STOOL SOFTENER	LIQUID	ORAL	Y
docusate sodium	COLACE	SYRUP	ORAL	Y
docusate sodium	DOCUSATE SODIUM	SYRUP	ORAL	Y
docusate sodium	PEDIA-LAX STOOL SOFTENER	SYRUP	ORAL	Y
docusate sodium	SILACE	SYRUP	ORAL	Y

docusate sodium	STOOL SOFTENER	SYRUP	ORAL	Y
docusate sodium	DOCUSATE SODIUM	TABLET	ORAL	Y
docusate sodium	DOK	TABLET	ORAL	Y
docusate sodium	STOOL SOFTENER	TABLET	ORAL	Y
fructooligosaccharides/polydex	FIBEREX F15	LIQUID	ORAL	Y
lactulose	CONSTULOSE	SOLUTION	ORAL	Y
lactulose	ENULOSE	SOLUTION	ORAL	Y
lactulose	GENERLAC	SOLUTION	ORAL	Y
lactulose	LACTULOSE	SOLUTION	ORAL	Y
magnesium citrate	CITRATE OF MAGNESIA	SOLUTION	ORAL	Y
magnesium citrate	MAGNESIUM CITRATE	SOLUTION	ORAL	Y
magnesium hydroxide	MILK OF MAGNESIA	ORAL SUSP	ORAL	Y
magnesium hydroxide	PEDIA-LAX	TAB CHEW	ORAL	Y
methylcellulose	CITRUCEL	TABLET	ORAL	Y
methylcellulose	FIBER	TABLET	ORAL	Y
methylcellulose	FIBER LAXATIVE	TABLET	ORAL	Y
methylcellulose	FIBER THERAPY	TABLET	ORAL	Y
methylcellulose (with sugar)	FIBER THERAPY	POWDER	ORAL	Y
polyethylene glycol 3350	CLEARLAX	POWDER	ORAL	Y
polyethylene glycol 3350	GAVILAX	POWDER	ORAL	Y
polyethylene glycol 3350	GLYCOLAX	POWDER	ORAL	Y
polyethylene glycol 3350	NATURA-LAX	POWDER	ORAL	Y
polyethylene glycol 3350	POLYETHYLENE GLYCOL 3350	POWDER	ORAL	Y
psyllium husk	FIBER	CAPSULE	ORAL	Y
psyllium husk	FIBER LAXATIVE	CAPSULE	ORAL	Y
psyllium husk	KONSYL	CAPSULE	ORAL	Y
psyllium husk	NATURAL FIBER	CAPSULE	ORAL	Y
psyllium husk	KONSYL	POWDER	ORAL	Y
psyllium husk	KONSYL EASY MIX	POWDER	ORAL	Y
psyllium husk (with dextrose)	KONSYL FORMULA-D	POWDER	ORAL	Y
psyllium husk (with sugar)	FIBER	POWDER	ORAL	Y
psyllium husk (with sugar)	KONSYL	POWDER	ORAL	Y
psyllium husk (with sugar)	NATURAL FIBER	POWDER	ORAL	Y
psyllium husk (with sugar)	NATURAL FIBER LAXATIVE	POWDER	ORAL	Y
psyllium husk (with sugar)	NATURAL VEGETABLE POWDER	POWDER	ORAL	Y
psyllium husk (with sugar)	REGULOID	POWDER	ORAL	Y
psyllium husk/aspartame	FIBER	POWDER	ORAL	Y
psyllium husk/aspartame	NATURAL FIBER	POWDER	ORAL	Y
psyllium seed	FIBER SMOOTH	POWDER	ORAL	Y
psyllium seed	KONSYL	POWDER	ORAL	Y

psyllium seed	NATURAL VEGETABLE LAXATIVE	POWDER	ORAL	Y
psyllium seed	NATURAL VEGETABLE POWDER	POWDER	ORAL	Y
psyllium seed	NVP	POWDER	ORAL	Y
psyllium seed	REGULOID	POWDER	ORAL	Y
psyllium seed (with dextrose)	KONSYL-D	PACKET	ORAL	Y
psyllium seed (with dextrose)	FIBER	POWDER	ORAL	Y
psyllium seed (with dextrose)	KONSYL-D	POWDER	ORAL	Y
psyllium seed (with dextrose)	MODANE BULK	POWDER	ORAL	Y
psyllium seed (with dextrose)	NATURAL FIBER	POWDER	ORAL	Y
psyllium seed (with dextrose)	NATURAL VEGETABLE POWDER	POWDER	ORAL	Y
psyllium seed (with sugar)	FIBER SMOOTH	POWDER	ORAL	Y
psyllium seed (with sugar)	NATURAL FIBER	POWDER	ORAL	Y
psyllium seed (with sugar)	NATURAL FIBER POWDER	POWDER	ORAL	Y
psyllium seed (with sugar)	NATURAL PSYLLIUM LAXATIVE	POWDER	ORAL	Y
psyllium seed (with sugar)	NATURAL VEGETABLE LAXATIVE	POWDER	ORAL	Y
psyllium seed (with sugar)	NVP	POWDER	ORAL	Y
psyllium seed/aspartame	KONSYL	POWDER	ORAL	Y
psyllium seed/aspartame	NATURAL FIBER	POWDER	ORAL	Y
psyllium seed/sod bicarb	KONSYL EFFERVESCENT	PACKET	ORAL	Y
senna leaf extract	SENNA	SYRUP	ORAL	Y
senna/psyllium seed	PERDIEM	GRANULES	ORAL	Y
sennosides	SENNA	CAPSULE	ORAL	Y
sennosides	SENNA	SYRUP	ORAL	Y
sennosides	CHOCOLATED LAXATIVE	TAB CHEW	ORAL	Y
sennosides	EX-LAX	TAB CHEW	ORAL	Y
sennosides	EX-LAX	TABLET	ORAL	Y
sennosides	EX-LAX MAXIMUM STRENGTH	TABLET	ORAL	Y
sennosides	LAXATIVE	TABLET	ORAL	Y
sennosides	LAXATIVE MAXIMUM STRENGTH	TABLET	ORAL	Y
sennosides	NATURAL VEGETABLE LAXATIVE	TABLET	ORAL	Y
sennosides	PERDIEM	TABLET	ORAL	Y
sennosides	SENEXTON	TABLET	ORAL	Y
sennosides	SENNA	TABLET	ORAL	Y
sennosides	SENNA LAX	TABLET	ORAL	Y
sennosides	SENNA LAXATIVE	TABLET	ORAL	Y
sennosides	SENNATURAL	TABLET	ORAL	Y
sennosides	SENNO	TABLET	ORAL	Y
sennosides	SEKOKOT	TABLET	ORAL	Y
sennosides/docusate sodium	COLACE 2-IN-1	TABLET	ORAL	Y
sennosides/docusate sodium	DOCUSATE SODIUM-SENNA	TABLET	ORAL	Y

sennosides/docusate sodium	DOK PLUS	TABLET	ORAL	Y
sennosides/docusate sodium	SENEXON-S	TABLET	ORAL	Y
sennosides/docusate sodium	SENNAPLUS	TABLET	ORAL	Y
sennosides/docusate sodium	SENNAS	TABLET	ORAL	Y
sennosides/docusate sodium	SENNATIME S	TABLET	ORAL	Y
sennosides/docusate sodium	SENNOSIDES-DOCUSATE SODIUM	TABLET	ORAL	Y
sennosides/docusate sodium	SENNOKOT-S	TABLET	ORAL	Y
sennosides/docusate sodium	STOOL SOFTENER-LAXATIVE	TABLET	ORAL	Y
sennosides/docusate sodium	STOOL SOFTENER-STIMULANT LAX	TABLET	ORAL	Y
sennosides/docusate sodium	VEGETABLE LAX-STOOL SOFTENER	TABLET	ORAL	Y
sennosides/psyllium husk	SENNAPROMPT	CAPSULE	ORAL	Y
wheat dextrin	BENEFIBER	POWD PACK	ORAL	Y
wheat dextrin	BEST FIBER	POWDER	ORAL	Y
alvimopan	ENTEREG	CAPSULE	ORAL	N
bran	BRAN	TABLET	ORAL	N
bran	OAT BRAN FIBER	TABLET	ORAL	N
casanthranol/docusate sodium	DOCUSATE SODIUM W/CASANTHRANOL	CAPSULE	ORAL	N
casanthranol/docusate sodium	DOCUSATE SODIUM-CASANTHRANOL	CAPSULE	ORAL	N
casanthranol/docusate sodium	PERI-COLACE	CAPSULE	ORAL	N
casanthranol/docusate sodium	STOOL SOFTENER W/LAXATIVE	CAPSULE	ORAL	N
casacara sagrada/mag hydrox	MILK OF MAGNESIA W/CASCARA	ORAL SUSP	ORAL	N
castor oil	CASTOR OIL	OIL	ORAL	N
dextrin	FIBER	POWDER	ORAL	N
lactulose	KRISTALOSE	PACKET	ORAL	N
linaclotide	LINZESS	CAPSULE	ORAL	N
lubiprostone	AMITIZA	CAPSULE	ORAL	N
methylcellulose	CITRUCEL	POWDER	ORAL	N
methylcellulose	FIBER THERAPY	POWDER	ORAL	N
methylcellulose (with sugar)	CITRUCEL	POWDER	ORAL	N
methylcellulose (with sugar)	FIBER THERAPY	POWDER	ORAL	N
methylnaltrexone bromide	RELISTOR	SYRINGE	SUB-Q	N
methylnaltrexone bromide	RELISTOR	TABLET	ORAL	N
methylnaltrexone bromide	RELISTOR	VIAL	SUB-Q	N
mineral oil	MINERAL OIL	OIL	ORAL	N
naldemedine tosylate	SYMPROIC	TABLET	ORAL	N
naloxegol oxalate	MOVANTIK	TABLET	ORAL	N
plecanatide	TRULANCE	TABLET	ORAL	N
polyethylene glycol 3350	CLEARLAX	POWD PACK	ORAL	N
polyethylene glycol 3350	HEALTHYLAX	POWD PACK	ORAL	N
polyethylene glycol 3350	POLYETHYLENE GLYCOL 3350	POWD PACK	ORAL	N

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polyethylene glycol 3350	SMOOTHLAX	POWD PACK	ORAL	N
psyllium husk	REGULOID	CAPSULE	ORAL	N
psyllium husk	KONSYL	POWD PACK	ORAL	N
psyllium husk (with sugar)	KONSYL	POWD PACK	ORAL	N
prucalopride succinate	MOTEGRITY	TABLET	ORAL	
tegaserod hydrogen maleate	ZELNORM	TABLET	ORAL	

## Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to December Week 1 2019, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 17, 2019

1. Bisacodyl/	163
2. Calcium polycarbophil.mp.	96
3. Cellulose/	15464
4. Docusate.mp. or Dioctyl Sulfosuccinic Acid/	406
5. Lactulose/	1012
6. Magnesium citrate.mp.	277
7. Magnesium Hydroxide/ or Aluminum Hydroxide/ or Calcium Carbonate/	6286
8. Methylcellulose/	1965
9. Polyethylene glycol.mp.	2
10. Psyllium.mp. or Psyllium/	497
11. Senna.mp. or Senna Extract/	536
12. Wheat dextrin.mp.	19
13. Alvimopan.mp.	196
14. Castor Oil/	511
15. Dextrins/	362
16. Lactulose/	1012
17. linaclotide.mp.	261
18. Lubiprostone/	153
19. Methylcellulose/	1965
20. methylnaltrexone.mp.	301
21. Mineral Oil/	643
22. naldemedine.mp.	39
23. naloxegol.mp.	99
24. plecanatide.mp.	56
25. Casanthranol.mp. or Cascara/	15
26. prucalopride.mp.	321
27. Sodium phosphate.mp.	3459
28. tegaserod.mp.	408
29. Gastrointestinal Motility/ or Irritable Bowel Syndrome/	12214
30. Constipation/	7872
31. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28	32566
32. 29 or 30	18976
33. 31 and 32	1199
34. limit 35 to (english language and humans and yr="2016 -Current" and (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or comparative study or meta-analysis or multicenter study or randomized controlled trial or "systematic review"))	71

## Drugs for Constipation

**Length of Authorization:**

- Up to 6 months

**Not Covered by OHP:**

- Disorders of function of stomach and other functional digestive disorders which includes constipation and Irritable Bowel Syndrome (ICD-10: K3183-3184, K310, R1110, K30, K3189, K319, K314-315, K312, K589, K591, K594, K5900-5902, K5909, K910-911, K9189, K598-599, R159, R150, R152)

**Requires PA:**

- Non-preferred drugs

**Covered Alternatives:**

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis covered by the OHP?	<b>Yes:</b> Go to #3	<b>No:</b> Pass to RPh. Deny; diagnosis not covered by OHP.
3. Will the prescriber consider a change to a preferred product?  Message: preferred products do not require a PA.	<b>Yes:</b> Inform prescriber of covered alternatives	<b>No:</b> Go to #4

## Approval Criteria

4. Has the patient failed a 2-week trial of at least 3 of the following management strategies due to lack of effectiveness, contraindications or adverse effects?

<b>A</b>	Dietary modification—increased dietary fiber (25 g/day)
<b>B</b>	Bulk-forming Laxatives: (psyllium [e.g., Metamucil], methylcellulose [e.g., Citrucel], calcium carbophil [e.g., Fibercon])
<b>C</b>	Saline Laxatives: (magnesium hydroxide [e.g., Milk of Magnesia], magnesium citrate, sodium phosphate [Fleet Enema])
<b>D</b>	Stimulant Laxatives: (senna or bisacodyl)
<b>E</b>	Osmotic Laxatives: (lactulose, sorbitol or polyethylene glycol 3350 [e.g., Miralax, Glycolax])

**Yes:** Approve for 6 months.

**No:** Pass to RPh. Go to #5.

## Approval Criteria

### 5. RPh only:

Constipation is not covered under the OHP. Therefore, funding for drugs that treat constipation are dependent whether the constipation adversely affects, or is secondary to, the underlying medical condition covered by the Prioritized List.

- Alvimopan (ENTEREG): FDA labeling, including a black boxed warning for risk of myocardial infarction, limit use to *in hospital use only* for a maximum of 15 doses. Evidence is primarily for the immediate post-operative period only.
- Linaclotide (LINZESS): Constipation secondary to irritable bowel syndrome is not approvable. Chronic constipation caused by a funded condition or adversely affecting a funded condition is approvable if medically appropriate and justification is provided for not meeting criterion #4.
- Lubiprostone (AMITIZA): Constipation secondary to irritable bowel syndrome or opioid-induced constipation is not approvable. Chronic constipation caused by a funded condition or adversely affecting a funded condition is approvable if medically appropriate and justification is provided for not meeting criterion #4.
- Methylnaltrexone (RELISTOR) and Naldemedine (SYMPROIC): Opioid-induced constipation in patients with non-cancer pain is not approvable. Chronic constipation secondary to continuous opioid use as part of a palliative care regimen is approvable if justification is provided for not meeting criterion #4.
- Naldemedine (SYMPROIC): Opioid-induced constipation in patients with non-cancer pain is not approvable. Justification must be provided for not meeting criterion #4.
- Naloxegol (MOVANTIK): Opioid-induced constipation in patients with non-cancer pain is not approvable. Justification must be provided for not meeting criterion #4.
- Plecanatide (TRULANCE): Chronic idiopathic constipation is not approvable. Chronic constipation caused by a funded condition or adversely affecting a funded condition is approvable if medically appropriate and justification is provided for not meeting criterion #4.
- Prucalopride (MOTEGRITY): Chronic idiopathic constipation is not approvable. Chronic constipation caused by a funded condition or adversely affecting a funded condition is approvable if medically appropriate and justification is provided for not meeting criterion #4.
- Tegaserod (ZELNORM): Constipation secondary to irritable bowel syndrome is not approvable. Justification must be provided for not meeting criterion #4.
- Tenapanor (ISBRELA): Constipation secondary to irritable bowel syndrome is not approvable. Justification must be provided for not meeting criterion #4.

P&T Review: [6/20 \(DM\)](#), 7/17 (DM); 3/15; 3/09  
Implementation: [TBD](#), 9/1/17; 5/1/16; 10/15, 4/18/15

## New Drug Evaluation: emapalumab-lzsg, injection

**Date of Review:** June 2020

**Generic Name:** emapalumab-lzsg

**End Date of Literature Search:** 10/09/19

**Brand Name (Manufacturer):** Gamifant (Novimmune SA)

**Dossier Received:** yes

### Research Questions:

1. What is the efficacy of emapalumab for the treatment of primary hemophagocytic lymphohistiocytosis (pHLH) with refractory, recurrent or progressive disease or intolerance to conventional HLH therapy?
2. Is emapalumab safe for the treatment of pHLH?
3. Are there subgroups of patients with pHLH for which emapalumab is more effective or associated with fewer adverse events?

### Conclusions:

- There is insufficient evidence from one unpublished, non-randomized open-label trial that emapalumab treatment resulted in a statistically significant overall response rate compared to placebo in pHLH patients intolerant or refractory to conventional therapy [63% (95% CI: 0.42 to 0.81;  $p=0.0134$ )].<sup>1</sup>
- Low quality evidence for safety of emapalumab over 8 weeks suggests risk for infections (56%), hypertension (41%), infusion-related reactions (27%), and pyrexia (24%).<sup>1,2</sup>
- There is insufficient evidence to evaluate the efficacy and safety of emapalumab beyond 8 weeks and to assess long-term clinical outcomes.<sup>1,2</sup>

### Recommendations:

- Create Preferred Drug List (PDL) class for Drugs for hemophagocytic lymphohistiocytosis (HLH).
- Designate emapalumab-lzsg as non-preferred.
- Implement clinical prior authorization for emapalumab to ensure appropriate utilization (**Appendix 2**)

### Background:

Hemophagocytic lymphohistiocytosis (HLH) is a rare and fatal syndrome of hyperinflammation, tissue damage, and multi-organ failure.<sup>3</sup> HLH is caused by defective cytotoxic T lymphocyte (CTL) and natural killer (NK) cell communication pathways which leads to excessive cytokine production, unregulated immune cell activation, and destructive macrophage accumulation in tissues and organs.<sup>3</sup> The abnormal immune response observed in HLH may originate from a primary genetic defect or be acquired secondary to an environmental trigger.<sup>4</sup> HLH typically manifests in infants and younger children up to 18 months; however, the disease may also present in adults and the elderly.<sup>5</sup> HLH patients commonly present with a high fever, cytopenia, coagulopathy, and hepatosplenomegaly with

lymphadenopathy. Up to 65% of pediatric HLH patients display a nonspecific macropapular rash as well.<sup>6</sup> Approximately 25-50% of primary HLH patients experience neurologic problems which range from headaches and irritability to encephalopathy, seizures, and coma.<sup>7</sup> As HLH progresses, patients exhibit further hepatic decline and neurologic complications with eventual multi-organ dysfunction and death.<sup>7</sup> If untreated, studies have shown patients with primary HLH (pHLH) have a median survival of roughly 2 months.<sup>8</sup> Therefore, most pHLH patients will eventually require allogeneic hematopoietic stem cell transplantation (HSCT) which improves 3-year survival rate from almost 0% to 50%.<sup>3,9</sup> The mortality rate for secondary acquired HLH is above 50%.<sup>8</sup> The overall incidence of HLH is estimated to be 12 per million worldwide and a prevalence of roughly 1 in 100,000 in the United States.<sup>10,11</sup> Within the past year, there were approximately 14 Oregon Medicaid patients with HLH-related claims and 3 were in the Fee-for-Service (FFS) program.

In normal immune function, cytotoxic T lymphocytes (CTLs), natural killer (NK), and T-regulatory cells control infection and inflammation through granule-mediated cytotoxicity.<sup>12</sup> Macrophages present foreign antigens to lymphocytes for direct termination and help stimulate the development of antibodies.<sup>13</sup> In HLH, there are defects in the signaling pathways and feedback loops that govern typical immune response.<sup>13</sup> With the inflammatory cascade left unchecked, lymphocytes and macrophages continue to proliferate and secrete high levels of pro-inflammatory cytokines such as interferon gamma, tumor necrosis factor-alpha, macrophage colony-stimulating factor, and several interleukins.<sup>14</sup> IFN-gamma is alleged to play a crucial role in macrophage hemophagocytosis while elevated TNF levels have been associated with increased hypofibrinogenemia and other blood dyscrasias.<sup>15,16</sup> The hyperactivated macrophages, NK cells, and CTLs, along with cytokine storm, is believed to be the origin of tissue damage and destruction.<sup>13</sup>

HLH is a heterogeneous spectrum of clinically similar subtypes, so it is often difficult for clinicians to differentiate from other infections, hematological malignancies, and cytokine storm syndromes.<sup>3,17</sup> When HLH presents in neonates, it may be overlooked and mistakenly treated as sepsis.<sup>3,18</sup> Children with an exaggerated response to infections along with extremely high cytokine levels and low/absent NK cell function are suspected to have HLH.<sup>3</sup> To facilitate a more rapid and specific diagnosis, the Histiocyte Society updated guidelines in 2004 to standardize HLH criteria.<sup>19</sup> A positive HLH diagnosis requires that 5 of 8 criteria be met (see **Table 1**) unless HLH is confirmed through genetic tests.<sup>19</sup> The diagnostic guidelines are mostly based on clinical experience with children but are commonly applied to all suspected HLH patients.<sup>9</sup>

**Table 1: Hemophagocytic Lymphohistiocytosis Diagnostic Criteria**<sup>19</sup>

<b>HLH diagnosis fulfilled if patients meet 5 out of 8 criteria listed below:</b>
Fever
Hemophagocytosis in bone marrow or spleen or lymph nodes
Low or absent NK-cell activity (according to local laboratory reference)
Ferritin $\geq 500$ $\mu\text{g/L}$
Soluble CD25 (i.e. soluble IL-2 receptor) $\geq 2,400$ U/mL
Splenomegaly
Hypertriglyceridemia and/or hypofibrinogenemia: Fasting triglycerides $\geq 3.0$ mmol/L ( $\geq 265$ mg/dL) or Fibrinogen $\leq 1.5$ g/L
Cytopenias (affecting $\geq 2$ of 3 lineages in the peripheral blood): Hemoglobin $< 90$ g/L (in infants $< 4$ weeks: hemoglobin $< 100$ g/L); Platelets $< 100 \times 10^9$ /L; Neutrophils $< 1.0 \times 10^9$ /L

Primary HLH (pHLH) is often connected with family history and/or a homozygous mutation.<sup>9</sup> Reactive, or secondary HLH (sHLH) is mostly acquired via immune activation usually provoked by infection, malignancy, metabolic conditions, or an underlying autoimmune/rheumatologic disorder.<sup>9,17</sup> Primary HLH may be further subclassified into familial lymphohistiocytosis (FHL) which is usually an autosomal recessive genetic mutation of one of 4 genes in the lymphocyte perforin pathway.<sup>9</sup> Primary HLH may also be associated with other immune function diseases.<sup>17,20</sup> Classification of various HLH subtypes are listed in **Table 2**. Secondary HLH is generally associated with underlying conditions such as severe infections, malignancies, or inflammatory disease.<sup>4,20</sup> Although pHLH has historically been exclusively associated with genetic mutation, recent evidence indicates the possibility of genetic predisposition in secondary HLH as well.<sup>21</sup> Knowledge of the patient’s genetic factors may help predict the chance of recurrence, need for HSCT, and future risk of HLH for family members.<sup>4,9,20</sup>

**Table 2. Classification of Primary and Secondary HLH**<sup>9</sup>

Classification	Subtype/Association	Etiology
Primary HLH	Familial HLH type 1	Unknown gene mutation
	Familial HLH type 2	PRF1 gene mutation
	Familial HLH type 3	UNC13D gene mutation
	Familial HLH type 4	STX11 gene mutation
	Familial HLH type 5	STXBP2 gene mutation
	Griscelli syndrome type 2	RAB27A gene mutation
	Chediak–Higashi syndrome	LYST gene mutation
	Hermansky–Pudlak syndrome type 2	AP3B1 gene mutation
	X-linked lymphoproliferative disease – Type 1	SH2D1A gene mutation
	X-linked lymphoproliferative disease – Type 2	XIAP gene mutation
Secondary HLH	Infection	Viral (EBV, CMV, etc.)
		Bacterial ( <i>Mycobacterium</i> , etc.)
		Fungal ( <i>Histoplasma</i> , etc.)
		Parasitic ( <i>Leishmania</i> , etc.)
	Malignancy	Lymphoma, leukemia, etc.
Autoimmune/Inflammatory diseases “Macrophage activation syndrome”	sJIA, SLE, Kawasaki disease, etc.	

Abbreviations: CMV = cytomegalovirus; EBV = Epstein-Barr virus; HLH = Hemophagocytic lymphohistiocytosis; SLE = systemic lupus erythematosus; sJIA = systemic juvenile idiopathic arthritis

Current treatment for HLH involves a multi-faceted approach with the inclusion of both immediate and long-term strategies.<sup>22</sup> Therapy options include immunosuppressants, immunomodulators, biologic response modifiers, treatment of underlying illness (if acquired HLH), and HSCT.<sup>19,22</sup> Ascertainment of disease etiology assists in the treatment plan, although in most cases, primary and secondary HLH generally follow the same initial protocol at the time of diagnosis.<sup>3</sup> The overarching goal is to suppress hyperinflammation and immune system dysfunction that decimates organs and leaves the patient vulnerable to deadly infections.<sup>23</sup> Infected macrophages must also be destroyed in order to halt the unregulated inflammatory cascade.<sup>3</sup> If pHLH has been confirmed, patients typically undergo 8 weeks induction phase of chemotherapy and immunotherapy to achieve remission followed by a continuation phase until HSCT.<sup>4</sup> Primary HLH patients unable to receive HSCT routinely yield to infections, bleeding, and/or multi-organ dysfunction and require intensive care and support due to

complications.<sup>3</sup> For acquired (secondary) HLH, identification and immediate treatment of the underlying infection, malignancy, or autoimmune disease is priority.<sup>24</sup>

Although there are no high-quality clinical guidelines for the treatment of HLH, in 1994, the Histiocyte Society presented a set of diagnostic and treatment protocols to assist in HLH management.<sup>25</sup> The protocol was updated in 2004 with minor changes; however, the agents and principles behind treatment have remained largely unchanged up to the present time.<sup>19,22</sup> In general, core HLH therapy has consisted of a combination of etoposide and dexamethasone at body surface area (BSA)-based doses administered at routine intervals in preparation for HSCT.<sup>14</sup> It has been demonstrated that the HLH-94 protocol has enabled over 71% of pHLH patients to survive to HSCT.<sup>23</sup> Etoposide is believed to induce activated T-cell death and suppress cytokine production while dexamethasone serves as important anti-inflammatory corticosteroid due to its long half-life and ability to concentrate in the cerebrospinal fluid.<sup>26,27</sup> Cyclosporine has often been incorporated into the 8-week induction regimen, but the timing and utility differs with respect to whether the HLH-94 or HLH-2004 protocol is used.<sup>4</sup> Immune globulins such as intravenous immunoglobulin have also shown some benefit in HLH treatment.<sup>28</sup> Direct evidence is limited for other immune-modulators and/or biological response modifiers such as rituximab, etanercept, infliximab, and alemtuzumab although some small observational studies have reported benefit.<sup>22,29,30</sup> **Table 3** is a summary of standard HLH therapy that have been used in large, multicenter trials sponsored by the Histiocyte Society.<sup>1,19</sup> It has been suggested that all primary genetic HLH patients and many secondary cases be treated with HSCT to improve outcomes.<sup>31,32</sup> Many studies have demonstrated HSCT to effectively control and possibly cure the disease altogether.<sup>31,32</sup>

**Table 3. Standard First-Line Therapy for Hemophagocytic Lymphohistiocytosis (HLH)<sup>1,19</sup>**

Regimen	Population	Dosing/Administration	Efficacy Information	Important Safety and Tolerability Issues
HLH-2004 N=369 N=168 with family history or genetically verified HLH	Previously untreated pediatric patients with pHLH	Initial: -Etoposide 150 mg/m <sup>2</sup> twice per week for 2 weeks then weekly for 6 weeks; -Dexamethasone 10 mg/m <sup>2</sup> /daily tapered every 2 weeks until week 8  Continuation until HSCT: -Dexamethasone pulses 10 mg/m <sup>2</sup> every 3 days every second week -Etoposide infusions 150 mg/m <sup>2</sup> every alternating second week -Cyclosporine orally daily (goal trough level: 200 mcg/L) -Methotrexate IT at a maximum of 4 doses only during weeks 3–6 if neurological symptoms progress during the first 2 weeks or if abnormal CSF at onset has not improved after 2 weeks -CSF analysis and brain MRI should be performed at new onset or reactivation of neurological symptoms	Response rates: not reported Survival to transplant: 81% OS (5-year): 61% (95% CI: 56% to 67%)	Addition of cyclosporine upfront did not improve outcomes – no longer recommended during induction

Abbreviations: CI=confidence interval; CSF=cerebrospinal fluid; HLH=hemophagocytic lymphohistiocytosis; HSCT= hematopoietic stem cell transplantation; IT= intrathecal; IV=intravenous; MRI = magnetic resonance imaging; OS=overall survival

**Clinical Efficacy:**

Emapalumab (Gamifant®) is a monoclonal antibody for the treatment of pHLH.<sup>1,2</sup> Emapalumab binds to the interferon gamma (IFN $\gamma$ ) receptor to neutralize free and receptor-bound IFN $\gamma$ .<sup>1,2</sup> The agent was designated a Breakthrough Therapy by the FDA and given priority review status in March of 2016. The drug was approved for the treatment of adult and pediatric pHLH in November 2018.<sup>1</sup> There are no other FDA-approved drugs for refractory, recurrent, or progressive pHLH or for those who are intolerant to conventional pHLH therapy.<sup>1</sup> Emapalumab is initially dosed at 1 mg/kg administered intravenously over 60 minutes twice weekly, titrated to 3, 6, or 10 mg/kg based on clinical response and laboratory parameters, then continued until HSCT or unacceptable toxicity.<sup>1,2</sup> Pharmacokinetic data demonstrated no need to adjust dose based on patient age, race, gender, renal or hepatic impairment.<sup>1,2</sup> See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, and use in specific populations.

There are currently no published studies available to evaluate the efficacy and safety of emapalumab, and therefore the risk of bias and financial disclosures could not be assessed. FDA Center for Drug Evaluation and Research review provided evidence for the efficacy summary. Given the rarity of pHLH, challenges in diagnosis and assessment, and the severity of clinical symptoms, the FDA reviewers determined that an adequately powered randomized controlled trial would be unfeasible.<sup>1</sup> Therefore, one 8-week, phase 2/3, multi-center, single-arm, non-randomized, open-label clinical trial was used for approval.<sup>1</sup> The study enrolled 34 patients: 27 had recurrent pHLH or refractory to standard treatment (second-line patients) and 7 were considered treatment naive (de novo) as determined by the physician.<sup>1,2</sup> Median age of subjects was 1 year, 53% were female, and 65% identified as White, 11% Asian, and 11% Black.<sup>1,2</sup> One-quarter of the subjects were from the United States.<sup>1,2</sup> The HLH diagnosis was based on genetic confirmation or fulfillment criteria as outlined by the Histiocyte Society (see **Table 1**).<sup>1</sup> Eighty-two percent of the patients had a genetic mutation recognized to cause HLH.<sup>1</sup> Patients with a diagnosis of secondary HLH consequent to a rheumatic or neoplastic disease were excluded as were those with active bacterial infections, malignancy, concomitant cardiovascular, pulmonary, liver, or renal disease.<sup>1</sup>

Emapalumab was administered as an intravenous infusion at 1 mg/kg every 3 to 4 days and was adjusted up to 10 mg/kg based on clinical response.<sup>1,2</sup> Almost half (44%) of the patients remained on the starting dose and the rest required a dose escalation.<sup>1</sup> All patients received concomitant dexamethasone therapy throughout the study.<sup>1,2</sup> Follow-up was for 1 year after transplant or last emapalumab dose.<sup>1</sup> The primary efficacy endpoint was overall response rate, defined as achievement of complete or partial response or HLH improvement at end of 8-week treatment or until HSCT if clinically warranted between 4 and 8 weeks.<sup>1,2</sup> See **Table 4** for summary of response rate definitions. The secondary outcomes included duration of response, percent of patients with steroid reduction, percent of patients proceeding to HSCT, and overall survival pre-and post-transplant.<sup>1</sup> Secondary outcomes were considered supportive and did not undergo formal statistical tests.<sup>1</sup>

**Table 4: Overall Response Rate Definitions<sup>1</sup>**

Overall Response Rate	
<b>Complete Response</b>	No fever (body temperature <37.5 ° C)
	Normal spleen size as measured by 3D abdominal ultrasound
	No cytopenia
	No hyperferritinemia
	No evidence of coagulopathy
	No neurological and CSF abnormalities attributed to HLH
	No sustained worsening of soluble interleukin-2 receptor (sCD25)

<b>Partial Response</b>	≥3 of the HLH clinical and laboratory abnormalities (including CNS abnormalities) met the aforementioned criteria for “complete response”
	In “reactivated patients” who entered the study with 3 abnormal HLH features, ≥2 criteria needed to meet the definition given
	There was no progression of other aspects of HLH disease pathology (e.g., jaundice, edema, CNS effects)
<b>HLH improvement</b>	Improvement (>50% change from baseline) of ≥3 HLH clinical and laboratory abnormalities (including CNS involvement)
	In “reactivated patients” who entered the study with 2 abnormal HLH features, a change from baseline greater than 50% for both defined HLH as improved

Abbreviations: CNS = central nervous system; CSF = cerebral spinal fluid; HLH = hemophagocytic lymphohistiocytosis

Thirty-four pHLH patients were treated with emapalumab, but FDA approval was based on efficacy results in only second-line patients intolerant or refractory to conventional therapy (n=27).<sup>1</sup> Of these 27 participants, 20 (74%) completed the study and the rest died.<sup>1,2</sup> The reported overall response rate was 63% (95% CI: 0.42 to 0.81; p=0.0134) with complete response reached by 26% of patients, partial response achieved by 30%, and HLH improvement achieved by 7%.<sup>1,2</sup> Nineteen of 27 (70%) patients proceeded to HSCT.<sup>1</sup>

There were limitations as to what conclusions could be drawn for emapalumab efficacy based on the data provided. The criteria to meet the definition of a patient with refractory, recurrent, or progressive pHLH was not specified but individually determined by the treating physician. In addition, the study outcome measures only applied to second-line treatment populations so the effects of emapalumab on treatment-naïve patients is unclear. Larger patient cohorts and more data are needed to determine the role of emapalumab in previously untreated patients. The data were insufficient to statistically evaluate secondary outcomes of response duration and overall survival. Although the investigators assessed time-to event endpoints with a Kaplan-Meier analysis, the reviewers were unable to interpret the findings due to the single arm trial design.

**Clinical Safety:**

The FDA clinical review analyzed safety data for all patients who had received emapalumab in the controlled study (n=34).<sup>1</sup> A total of 10 of the 34 treated patients died. In the primary efficacy cohort, 7 of the 27 (26%) patients died and six of those deaths occurred while in active treatment with emapalumab. Over half of the deaths were in patients who had developed a new infection or a deterioration of a pre-existing infection. Two fatalities (6%) were due to gastrointestinal hemorrhage and septic shock.<sup>1</sup> Other adverse effects associated with emapalumab during clinical trials included hypertension, infusion-related reactions, and pyrexia.<sup>1,2</sup> Incidence of adverse effects that occurred more frequently than 10% are outlined in **Table 5**.<sup>1,2</sup> The serious adverse events (SAEs) reported in 53% of patients were most commonly related to infections (32%), gastrointestinal hemorrhage (9%), and multiple organ dysfunction (6%).<sup>1,2</sup> Serious infections included sepsis, pneumonia, bacteremia, disseminated histoplasmosis, necrotizing fasciitis, and perforated appendicitis.<sup>1</sup> There were 9 patients (27%) that reported infusion-related reactions within 24 hours of emapalumab administration, but none were graded as severe and none led to discontinuations.<sup>1</sup> Due to the infection risk, manufacturer labeling recommends that patients be monitored for tuberculosis (TB), adenovirus, cytomegalovirus (CMV), and Epstein-Barr virus (EBV) every 2-weeks and as clinically indicated.<sup>2</sup>

**Table 5. Adverse Reactions Reported in ≥ 10% of Patients with Primary HLH<sup>1,2</sup>**

<b>Adverse Reactions</b>	<b>GAMIFANT (%) (N = 34)</b>
Infections <sup>a</sup>	56
Hypertension <sup>b</sup>	41
Infusion-related reactions <sup>c</sup>	27
Pyrexia	24
Hypokalemia	15
Constipation	15
Rash	12
Abdominal pain	12
Cytomegalovirus infection	12
Diarrhea	12
Lymphocytosis	12
Cough	12
Irritability	12
Tachycardia	12
Tachypnea	12

<sup>a</sup>Includes viral (30%), bacterial (15%), fungal (15%), and infections in which no pathogen was identified

<sup>b</sup>Includes secondary hypertension

<sup>c</sup>Includes events of drug eruption, pyrexia, rash, erythema, and hyperhidrosis

**Comparative Endpoints:**

Clinically Meaningful Endpoints:

- 1) Quality of life
- 2) Improved function
- 3) Survival
- 4) Serious adverse events
- 5) Study withdrawal due to an adverse event

Primary Study Endpoint:

- 1) Overall response rate
- 2) HLH improvement

**Table 6. Pharmacology and Pharmacokinetic Properties.<sup>1,2</sup>**

<b>Parameter</b>	
Mechanism of Action	Monoclonal antibody that binds to and neutralizes interferon gamma which is hypersecreted in HLH
Oral Bioavailability	N/A
Distribution and Protein Binding	4.2 L central; 5.6 L peripheral. Protein binding not evaluated (not expected to bind to plasma proteins).
Elimination	0.007 Liters/hour
Half-Life	22 days in healthy subjects; 2.5 to 18.9 days in HLH patients
Metabolism	Degraded into small peptides and amino acids via catabolic pathways

Abbreviations: HLH=hemophagocytic lymphohistiocytosis

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## Appendix 1: Prescribing Information Highlights

### HIGHLIGHTS OF PRESCRIBING INFORMATION

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

**GAMIFANT™ (emapalumab-lzsg) injection, for intravenous use**  
**Initial U.S. Approval: 2018**

#### INDICATIONS AND USAGE

GAMIFANT is an interferon gamma (IFN $\gamma$ ) blocking antibody indicated for the treatment of adult and pediatric (newborn and older) patients with primary hemophagocytic lymphohistiocytosis (HLH) with refractory, recurrent or progressive disease or intolerance with conventional HLH therapy. (1)

#### DOSAGE AND ADMINISTRATION

For intravenous infusion only:

- Recommended starting dosage: 1 mg/kg as an intravenous infusion over 1 hour twice per week. (2.1)
- Administer dexamethasone concomitantly with GAMIFANT. (2.3)

#### DOSAGE FORMS AND STRENGTHS

Injection:

- 10 mg/2 mL (5 mg/mL) solution in a single-dose vial (3)
- 50 mg/10 mL (5 mg/mL) solution in a single-dose vial (3)

#### CONTRAINDICATIONS

- None. (4)

#### WARNINGS AND PRECAUTIONS

- Infections: Monitor patients for signs and symptoms and treat promptly. Test for latent tuberculosis. Administer prophylactic treatment against Herpes Zoster, *Pneumocystis jirovecii* and fungal infections. (5.1)
- Live Vaccines: Do not administer live or live attenuated vaccines to patients receiving GAMIFANT. (5.2)
- Infusion-Related Reactions: Monitor patients for infusion-related reactions. Interrupt infusion for severe infusion reactions and institute appropriate medical management. (5.3)

#### ADVERSE REACTIONS

The most common adverse reactions ( $\geq 20\%$ ) were: infections, hypertension, infusion-related reactions, and pyrexia. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact 1-866-773-5274 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

**See 17 for PATIENT COUNSELING INFORMATION**

**Revised: 11/2018**

## Emapalumab

**Goal(s):**

- To ensure appropriate use of emapalumab in patients with primary hemophagocytic lymphohistiocytosis (pHLH).

**Length of Authorization:**

- 2 - 6 months

**Requires PA:**

- Emapalumab

**Covered Alternatives:**

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

**Table 1: Diagnostic Criteria for pHLH**

≥ 5 of the following 8 criteria at baseline	Fever
	Splenomegaly
	Cytopenias (2 or more): - Hemoglobin <9 g/dL (infants <4 weeks: <10 g/dL) - Platelets <100 x 10 <sup>9</sup> /L - Neutrophils <1 x 10 <sup>9</sup> /L
	Hypertriglyceridemia (fasting, >265 mg/dL) or hypofibrinogenemia (<150 mg/dL)
	Hemophagocytosis in spleen, bone marrow, lymph nodes or liver
	Low or absent NK cell activity
	Ferritin >500 µg/L
	Elevated soluble CD25 (interleukin 2 receptor alpha) ≥2,400 units/mL
<b>OR</b>	
Molecular Genetic Testing	Biallelic pathogenic gene variant (eg. <i>PRF1</i> , <i>UNC13D</i> , <i>STX11</i> , or <i>STXBP2</i> ) or family history consistent with primary HLH

**Table 2: Dosage and Administration**

Indication	Dosing Regimen	Maximum Dose
Primary HLH	1 mg/kg IV twice per week (every 3 to 4 days)	10 mg/kg/dose

Approval Criteria		
1. Is this a request for continuation of therapy previously approved by the FFS program?	<b>Yes:</b> Go to <b>Renewal Criteria</b>	<b>No:</b> Go to #2
2. What diagnosis is being treated?	Record ICD10 code.	
3. Is the diagnosis funded by OHP?	<b>Yes:</b> Go to #4	<b>No:</b> Pass to RPh. Deny; not funded by the OHP.
4. Is this agent being prescribed for treatment of refractory, recurrent, or progressive primary HLH or for those who are intolerant to conventional primary HLH therapy?  <i>Conventional therapy should have included an etoposide and dexamethasone-based regimen</i>	<b>Yes:</b> Document prior therapies or reasons for failure.  Go to #5	<b>No:</b> Pass to RPh. Deny; medical appropriateness.
5. Has the diagnosis of pHLH been confirmed by genetic testing or by diagnostic criteria listed in <b>Table 1</b> ?	<b>Yes:</b> Go to #6	<b>No:</b> Pass to RPh. Deny; medical appropriateness.
6. Is the agent prescribed by or in consultation with a specialist (e.g. hematologist) with experience in treating HLH patients?	<b>Yes:</b> Go to #7	<b>No:</b> Pass to RPh. Deny; medical appropriateness.
7. Is the agent being prescribed concurrently with dexamethasone?	<b>Yes:</b> Go to #8	<b>No:</b> Pass to RPh. Deny; medical appropriateness.
8. Is there documentation that the prescriber has assessed the patient and found no evidence of active infection?	<b>Yes:</b> Go to #9	<b>No:</b> Pass to RPh. Deny; medical appropriateness.
9. Has the patient received prophylaxis for Herpes Zoster, <i>Pneumocystis Jirovecii</i> , and fungal infections?	<b>Yes:</b> Go to #10	<b>No:</b> Pass to RPh. Deny; medical appropriateness.

<b>Approval Criteria</b>		
10. Is there documentation that the patient has been evaluated and will continue to be monitored for TB, adenovirus, EBV, and CMV every 2 weeks as clinically appropriate?	<b>Yes:</b> Go to #11	<b>No:</b> Pass to RPh. Deny; medical appropriateness.
11. Is the agent dosed appropriately based on documentation of a recent patient weight (see <b>Table 2</b> above)?	<b>Yes:</b> Document patient weight and go to #12  Weight:_____	<b>No:</b> Pass to RPh. Deny; medical appropriateness.
12. Is there attestation that the patient and provider will comply with case management to promote the best possible outcome for the patient and adhere to monitoring requirements required by the Oregon Health Authority?	<b>Yes:</b> Approve for 2 months.	<b>No:</b> Pass to RPh. Deny; medical appropriateness.

<b>Renewal Criteria</b>		
1. Does the patient show evidence of developing any serious infections, severe infusion reactions, or unacceptable toxicity related to emapalumab treatment/administration?	<b>Yes:</b> Pass to RPh. Deny; medical appropriateness	<b>No:</b> Go to #2
2. Is emapalumab being prescribed concurrently with dexamethasone?	<b>Yes:</b> Go to #3	<b>No:</b> Pass to RPh. Deny; medical appropriateness
3. Is the patient receiving ongoing monitoring for TB, adenovirus, EBV, and CMV every 2 weeks as clinically appropriate?	<b>Yes:</b> Go to #4	<b>No:</b> Pass to RPh. Deny; medical appropriateness
4. Does the provider attest that the patient has not yet received hematopoietic stem cell transplantation (HSCT)?	<b>Yes:</b> Go to #5	<b>No:</b> Pass to RPh. Deny; medical appropriateness

## Renewal Criteria

5. Has the patient's condition stabilized or improved as assessed by the prescribing provider?

**Yes:** Approve for up to 6 months.

**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 6/20 (DE)  
Implementation: TBD