Drug Use Research & Management Program
OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, June 3rd, 2021 12:00 - 5:00 PM
Remote Meeting via Zoom Platform
MEETING AGENDA

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

I. CALL TO ORDER

1:00 PM	A. Roll Call & Introductions	R. Citron (OSU)
	B. Approval of Agenda	R. Citron (OSU)
	C. Conflict of Interest Declaration	R. Citron (OSU)
	D. Approval of Minutes	R. Citron (OSU)
	E. Department Update	D. Weston (OHA)
	F. Legislative Update	T. Douglass (OHA)
1:20 PM	II. CONSENT AGENDA TOPICS	S. Ramirez (Chair)

A. Quarterly Utilization Reports
B. Colony Stimulating Factors Literature Scan
C. Oncology Prior Authorization Updates
D. Orphan Drug Policy Updates
   1. Public Comment

III. DUR ACTIVITIES

1:25 PM	A. ProDUR Report	R. Holsapple (Gainwell)
	1. Drug-drug interactions	
	2. Public comment	
	3. Recommendations to OHA	
	B. RetroDUR Report	D. Engen (OSU)
	C. Oregon State Drug Review	K. Sentena (OSU)
	1. Covid-19 Viral Testing	
	2. 2019-2020 Food and Drug Administration Drug Safety Communications Update	
	3. Coronavirus Disease-2019 Vaccine Update	

IV. DUR OLD BUSINESS

1:40 PM	A. Antipsychotics in Young Children Safety Edit 1. Prospective Safety Edit 2. Retrospective Safety Program 3. Public Comment 4. Discussion of Clinical Recommendations to OHA	S. Servid (OSU)
	V. PREFERRED DRUG LIST NEW BUSINESS	
1:55 PM	A. Growth Hormones Abbreviated Drug Review and Prior Authorization Update 1. Sogroya® (somapacitan-beco) Abbreviated Drug Review 2. Prior Authorization Criteria Update 3. Public Comment 4. Discussion of Clinical Recommendations to OHA	D. Engen (OSU)
2:05 PM	B. Hereditary Angioedema Class Update and New Drug Evaluation 1. Orladeyo™ (berotralstat) New Drug Evaluation 2. Class Update/Prior Authorization Criteria 3. Public Comment 4. Discussion of Clinical Recommendations to OHA	S. Servid (OSU)
2:20 PM	C. Multiple Sclerosis Class Update and New Drug Evaluations 1. Class Update/Prior Authorization Criteria 2. Kesimpta® (ofatumumab) New Drug Evaluation 3. Ponvory™ (ponesimod) New Drug Evaluation 4. Public Comment 5. Discussion of Clinical Recommendations to OHA	D. Moretz (OSU)
2:50 PM	BREAK	
3:05 PM	D. Focused Heart Failure Class Update with New Drug Evaluation 1. Entresto® (sacubitril/valsartan) Update 2. Verquvo® (vericiguat) New Drug Evaluation 3. Prior Authorization Criteria 4. Public Comment 5. Discussion of Clinical Recommendations to OHA	M. Herink (OSU)
3:25 PM	E. Platelet Inhibitors Class Update 1. Class Update/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	K. Sentena (OSU)
	VI. DUR NEW BUSINESS	
3:40 PM	A. Migraine Medications Drug Use Evaluation 1. Drug Use Evaluation 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	R. Bartholomew (OSU) M. Herink (OSU) S. Fletcher (OSU)

4:00pm	B. Cystic Fibrosis Prior Authorization Update 1. Prior Authorization Update 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	M. Herink (OSU)
4:05 PM	VII. EXECUTIVE SESSION	
4:50 PM	VIII. RECONVENE for PUBLIC RECOMMENDATIONS	
5:00PM	IX. ADJOURN	

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

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

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Thursday, April 01, 2021 1:00 - 5:00 PM

Via Zoom webinar

MEETING MINUTES

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

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

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

Audience: Amber Mayzak, Pharmayclics; Andrea Willcuts, Takeda; Becky Gonzales, ViiV Healthcare; BingBing Liang, CareOregon; **Boman Irani, Rhythm Pharmaceuticals*;** Brad Brekke, Rhythm Pharmaceuticals; Brandie Ferger, Advanced Health CCO; Chi Kohlhoff, Viela Bio; Corrine Anway, OSU; **Dale Edberg, Horizon Therapeutics*;** Dave Riepe, Merck; Dennis Schaffner, Sanofi Genzyme; Donald Nopper; Apellis Pharma; Erick Nash, Covis Pharma; Janeen McBride; **Jenny Todenhagen, Genentech*;** Jeremy Strand; Alexion; Jim Graves, BMS; Kapeka Kast, PCYC; Katie Scheelar, EOCCO/Moda Health; Keely Larson, Bayer; Laura Jeffcoat, Abbvie; Maggie Murphy, Teva Pharmaceuticals; Matt Worthy, OHSU, Matthew Wright, Artia Solutions; Timothy McFerron, Alkermes; Melissa Snider, Gilead; Michael Foster, BMS; Mike Nicholson; Paul Thompson, Alkermes; Pauline Whelan; **Raffaella Colzani, MD, Sanofi Genzyme*; Shannon Zandy, Alexion Pharmaceuticals*;** Tiffany Jones, PacificSource; Tracey Harrah, AVEO Oncology; Lori McDermott, Supernus; Norm Navarro, Providence; **Amy Yang, MD, OHSU*.**

(*) Provided verbal testimony

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Written testimony: Posted to OSU Website

I. CALL TO ORDER

A. The meeting was called to order at approximately 1:06 pm. Introductions were made by Committee members and staff
B. Conflict of Interest Declaration
C. Approval of February 2021 minutes presented by Mr. Citron
ACTION: Motion to approve, 2nd, all in favor
D. Department and legislative updates provided by Dee Weston

II. CONSENT AGENDA TOPICS

A. Oncology Prior Authorization Update
ACTION: Motion to approve, 2nd, all in favor

III. DUR NEW BUSINESS

A. **Opioid Class Literature Scan:** Andrew Gibler, PharmD
Policy Evaluation: Sarah Servid, PharmD
OHA Minimum Standard: Dee Weston
Recommendations:
- Update current policy with newly approved drug products
- Modify high-risk opioid RetroDUR program criteria to include patients who may be paying cash for chronic opioid prescriptions and patients with a diagnosis of substance abuse or history of overdose
-Notify providers about risk mitigation strategies and opportunities to improve care
ACTION: The Committee recommended adding an assessment for OUD in the renewal criteria for both short-acting and long-acting PA criteria
Motion to approve, 2nd, all in favor, one abstained

B. **Antipsychotics in Children Drug Effectiveness Review Project (DERP) Summary:** Sara Fletcher, PharmD
Mental Health Polypharmacy Drug Use Evaluation: Sarah Servid, PharmD
Recommendations:
- No PDL changes recommended based on the clinical evidence
- Evaluate costs in executive session

- Review profiles of patients with the following high-risk categories to identify opportunities for therapy optimization or de-prescribing: long-term use multiple mental health drugs; patients with possible contraindications to therapy; and very young children

ACTION:

The Committee requested staff bring back proposed safety-edit criteria to ensure appropriate use of antipsychotics for members less than five years old when initiating therapy with an antipsychotic and to require psychiatric/specialty consultation. The Committee also recommended identifying provider education opportunities to address off-label use of antipsychotics in kids and pursue strategies to notify prescribers

Motion to approve, 2nd, all in favor

IV. PREFERRED DRUG LIST NEW BUSINESS

A. **Imcivree™ (setmelanotide) Abbreviated Drug Review (ADR):** Sara Fletcher**,** PharmD
State Plan Overview of Excluded Drugs: Dee Weston, JD
Recommendation:
- Continue to designate setmelanotide as not covered per Oregon Medicaid State Plan
Public Comment: Boman Irani, Rhythm Pharmaceuticals
ACTION: Motion to approve, 2nd, all in favor

B. **Lumizyme® (alglucosidase alfa) New Drug Evaluation (NDE):** David Engen, PharmD
Recommendations:
- Add alglucosidase alfa to the lysosomal storage disorders PDL class and designate as non-preferred
- Implement proposed alglucosidase alfa PA criteria to ensure medically appropriate use
Public Comment: Raffaella Colzani, MD, Sanofi Genzyme; Amy Yang, MD, OHSU
ACTION: Motion to approve, 2nd, all in favor

C. **Statins: Class Update:** Megan Herink, PharmD
Recommendations:
- Continue to maintain preferred low-, moderate- and high-intensity statins
- Combine high-potency and low-medium potency PDL classes into one PDL statin class
- Evaluate costs in executive session
ACTION: Motion to approve, 2nd, all in favor

D. **Neuromyelitis Optica Spectrum Disorder (NMOSD) Class Review:**
Deanna Moretz, PharmD
Recommendations:
- Add the "Biologics for Rare Diseases" class to the PDL and include inebilizumab and satralizumab

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- Implement proposed PA criteria for each biologic agent
- Evaluate costs in executive session

Public Comment: Dale Edberg, PhD, Horizon Therapeutics; Jenny Todenhagen, Genentech

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

E. **Monoclonal Antibody C5 Inhibitors Class Review:** Deanna Moretz, PharmD

Recommendation:

- Add eculizumab and ravulizumab to the "Biologics for Rare Diseases" PDL class
- Implement proposed PA criteria for each biologic agent
- Evaluate costs in executive session

Public Comment: Shannon Zandy, Alexion Pharmaceuticals

ACTION: The Committee recommended adding age to the PA criteria for ravulizumab and to clarify that vaccination for meningitis should be given according to CDC guidance

Motion to approve, 2nd, all in favor

V. EXECUTIVE SESSION

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

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

VI. RECONVENE for PUBLIC RECOMMENDATIONS

A. **Second Generation Antipsychotics:**
Recommendation: No changes to the PDL are recommended

B. **Biologics for Rare Diseases: NMOSD treatments and C5 Inhibitors:**
Recommendation: Make eculizumab non-preferred; Make ravulizumab, satralizumab, and inebilizumab preferred

C. **Statins Class update**:
Recommendation: Make rosuvastatin tablets preferred
ACTION: Motion to approve, 2nd, all in favor

VII. ADJOURN

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Oregon State University
College of Pharmacy

Pharmacy Utilization Summary Report: October 2019 - September 2020

Eligibility	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Avg Monthly
Total Members (FFS & Encounter)	985,585	983,689	987,294	994,279	996,305	1,000,312	1,026,262	1,039,871	1,052,702	1,065,127	1,078,611	1,091,643	1,025,140
FFS Members	93,871	98,749	99,972	99,615	99,252	99,928	109,012	94,359	89,482	92,036	97,318	96,060	97,471
OHP Basic with Medicare	9,067	9,362	9,174	8,622	8,495	7,620	7,613	7,275	7,121	7,235	7,333	7,140	8,005
OHP Basic without Medicare	11,869	12,431	12,040	11,882	11,860	11,739	11,470	11,412	11,281	11,469	11,624	11,493	11,714
ACA	72,935	76,956	78,758	79,111	78,897	80,569	89,929	75,672	71,080	73,332	78,361	77,427	77,752
Encounter Members	891,714	884,940	887,322	894,664	897,053	900,384	917,250	945,512	963,220	973,091	981,293	995,583	927,669
OHP Basic with Medicare	69,151	68,769	69,265	69,949	70,261	71,185	71,584	72,135	72,516	72,537	72,713	73,520	71,132
OHP Basic without Medicare	62,079	62,180	62,716	62,920	62,837	62,961	63,059	62,873	62,810	62,587	64,059	65,009	63,008
ACA	760,484	753,991	755,341	761,795	763,955	766,238	782,607	810,504	827,894	837,967	844,521	857,054	793,529

Gross Cost Figures for Drugs	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	YTD Sum
Total Amount Paid (FFS & Encounter)	$88,435,881	$78,972,311	$85,068,349	$88,548,463	$83,441,470	$97,670,132	$85,470,546	$82,081,335	$88,795,487	$90,609,255	$88,050,657	$88,679,310	$1,045,823,197
Mental Health Carve-Out Drugs	$8,948,753	$8,124,821	$8,832,046	$9,314,467	$8,619,923	$9,529,724	$9,057,096	$8,784,838	$9,439,192	$9,470,921	$9,178,038	$9,239,606	$108,539,425
OHP Basic with Medicare	$39,134	$33,985	$42,387	$39,771	$32,745	$32,473	$30,950	$30,707	$36,154	$33,286	$31,662	$38,437	$421,691
OHP Basic without Medicare	$3,526,826	$3,185,686	$3,467,344	$3,663,991	$3,322,300	$3,685,868	$3,477,053	$3,282,535	$3,643,262	$3,564,617	$3,591,876	$3,569,752	$41,981,109
ACA	$5,335,416	$4,862,493	$5,267,827	$5,555,080	$5,207,588	$5,753,102	$5,501,114	$5,420,472	$5,713,623	$5,831,287	$5,504,846	$5,581,756	$65,534,603
FFS Physical Health Drugs	$2,924,613	$2,574,292	$2,718,902	$3,113,216	$2,797,758	$3,062,191	$2,915,932	$2,527,677	$2,569,997	$2,561,055	$2,374,187	$2,485,293	$32,625,114
OHP Basic with Medicare	$64,831	$56,764	$59,469	$63,985	$53,501	$60,396	$52,603	$44,203	$52,145	$56,272	$48,375	$48,169	$660,712
OHP Basic without Medicare	$1,097,706	$862,835	$915,467	$1,114,884	$1,003,800	$1,087,659	$1,003,799	$909,193	$912,908	$870,940	$849,072	$867,718	$11,495,981
ACA	$1,602,656	$1,522,541	$1,613,288	$1,778,387	$1,600,863	$1,774,799	$1,740,154	$1,451,622	$1,462,523	$1,485,686	$1,350,173	$1,439,780	$18,822,471
FFS Physician Administered Drugs	$1,511,491	$1,343,531	$1,304,240	$1,423,498	$1,707,028	$1,565,009	$1,164,128	$1,187,236	$1,391,437	$1,572,609	$1,151,484	$1,021,552	$16,343,242
OHP Basic with Medicare	$184,061	$144,249	$145,209	$150,069	$114,859	$91,816	$124,891	$118,571	$75,589	$129,482	$100,775	$105,609	$1,485,180
OHP Basic without Medicare	$413,746	$383,346	$242,341	$263,561	$618,689	$313,089	$141,949	$365,022	$459,854	$495,709	$239,627	$183,506	$4,120,440
ACA	$408,405	$434,162	$477,708	$560,893	$517,312	$432,552	$484,282	$333,434	$364,136	$390,815	$371,074	$368,515	$5,143,288
Encounter Physical Health Drugs	$59,499,560	$53,102,599	$56,841,769	$58,230,612	$55,184,236	$65,723,780	$57,842,717	$55,060,511	$58,944,609	$61,188,739	$59,559,267	$60,358,173	$701,536,574
OHP Basic with Medicare	$818,037	$757,073	$713,998	$852,257	$715,567	$843,938	$677,050	$676,669	$742,643	$689,876	$673,878	$783,905	$8,944,890
OHP Basic without Medicare	$14,340,973	$13,212,879	$14,164,619	$14,133,400	$13,299,765	$15,391,365	$14,121,803	$13,234,122	$14,106,678	$14,072,862	$14,366,587	$14,695,846	$169,140,900
ACA	$43,725,414	$38,595,247	$41,295,692	$42,564,769	$40,556,559	$48,704,374	$42,453,127	$40,517,325	$43,512,164	$45,795,752	$43,858,092	$44,239,850	$515,818,365
Encounter Physician Administered Drugs	$15,551,464	$13,827,069	$15,371,391	$16,466,671	$15,132,526	$17,789,428	$14,490,672	$14,521,073	$16,450,252	$15,815,931	$15,787,681	$15,574,685	$186,778,843
OHP Basic with Medicare	$608,979	$567,601	$559,005	$599,130	$573,982	$611,184	$493,219	$589,933	$619,269	$652,715	$605,935	$630,765	$7,111,716
OHP Basic without Medicare	$3,345,453	$2,705,663	$3,239,309	$3,692,099	$3,702,325	$3,463,812	$3,562,419	$3,397,652	$3,533,430	$3,185,860	$3,399,817	$3,583,839	$40,811,678
ACA	$11,272,447	$10,093,398	$11,047,690	$11,740,792	$10,599,129	$13,473,305	$10,232,131	$10,225,377	$11,916,916	$11,612,354	$11,435,833	$10,893,280	$134,542,651

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 22, 2021

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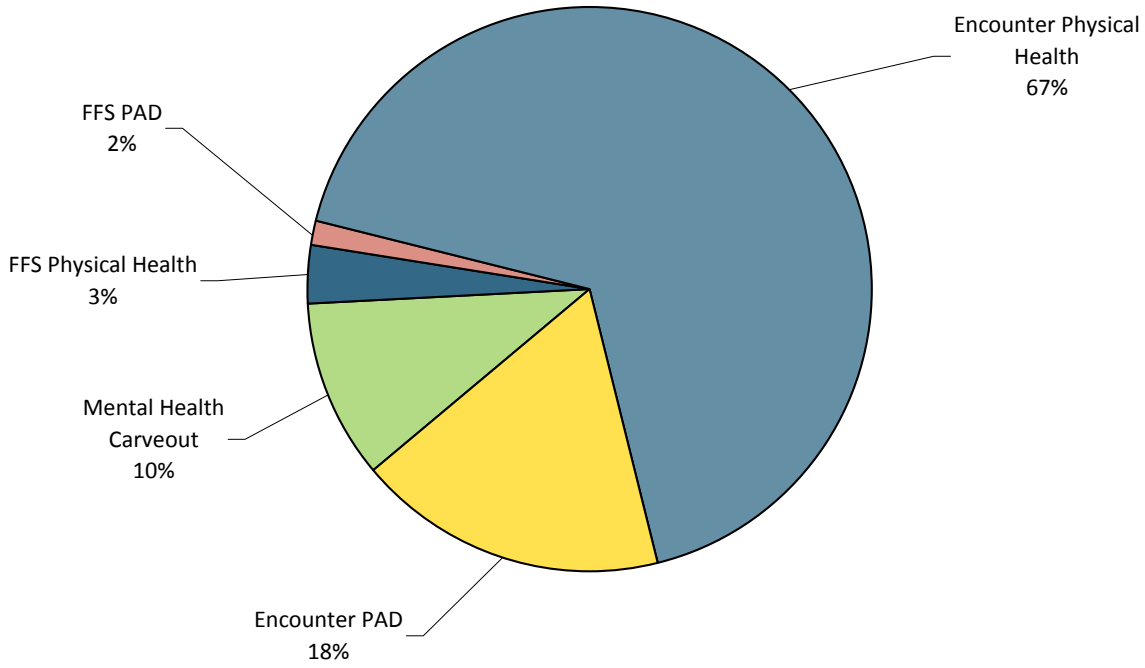
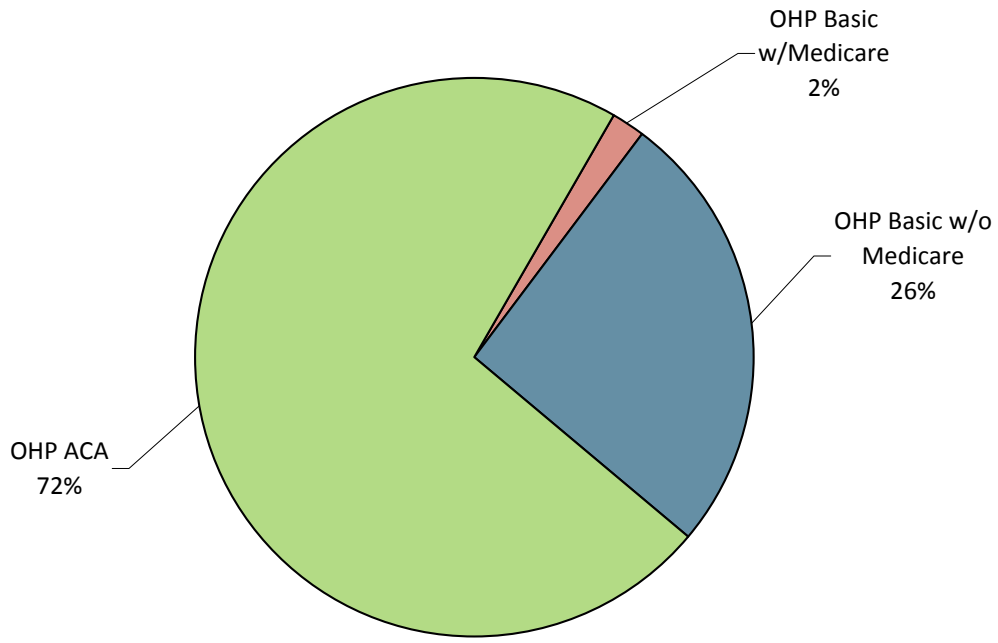
Pharmacy Utilization Summary Report: October 2019 - September 2020

YTD Percent Paid Amounts





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

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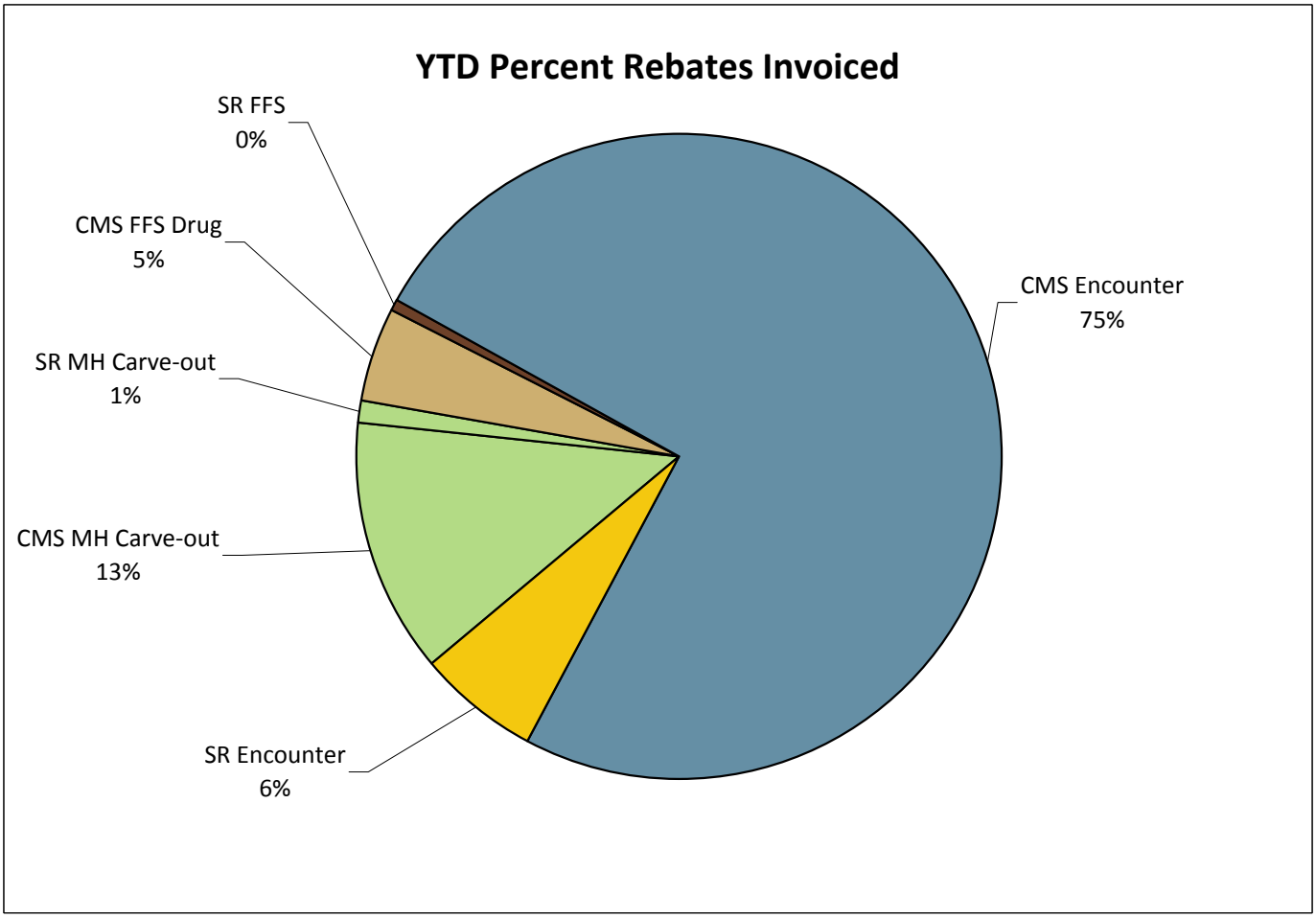
Pharmacy Utilization Summary Report: October 2019 - September 2020

Quarterly Rebates Invoiced	2019-Q4	2020-Q1	2020-Q2	2020-Q3	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$104,596,664	$114,394,528	$108,521,528	$116,366,042	$443,878,762
CMS MH Carve-out	$11,478,914	$13,592,128	$12,819,624	$18,668,814	$56,559,480
SR MH Carve-out	$1,269,765	$1,408,756	$1,330,995	$1,335,826	$5,345,342
CMS FFS Drug	$4,993,195	$5,901,576	$5,402,695	$4,683,060	$20,980,525
SR FFS	$329,652	$417,304	$473,719	$457,371	$1,678,047
CMS Encounter	$81,456,910	$86,191,923	$81,430,206	$83,694,622	$332,773,660
SR Encounter	$5,068,228	$6,882,841	$7,064,289	$7,526,350	$26,541,709

Quaterly Net Drug Costs	2019-Q4	2020-Q1	2020-Q2	2020-Q3	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$147,879,877	$155,265,537	$147,825,840	$150,973,180	$601,944,435
Mental Health Carve-Out Drugs	$13,156,941	$12,463,229	$13,130,507	$7,883,925	$46,634,603
FFS Phys Health + PAD	$7,054,221	$7,349,820	$5,879,993	$6,025,750	$26,309,784
Encounter Phys Health + PAD	$127,668,714	$135,452,489	$128,815,339	$137,063,505	$529,000,048



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

Last Updated: April 22, 2021

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Pharmacy Utilization Summary Report: October 2019 - September 2020

Gross PMPM Drug Costs (Rebates not Subtracted)	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$89.73	$80.28	$86.16	$89.06	$83.75	$97.64	$83.28	$78.93	$84.35	$85.07	$81.63	$81.23	$85.09
Mental Health Carve-Out Drugs	$9.08	$8.26	$8.95	$9.37	$8.65	$9.53	$8.83	$8.45	$8.97	$8.89	$8.51	$8.46	$8.83
FFS Physical Health Drugs	$31.16	$26.07	$27.20	$31.25	$28.19	$30.64	$26.75	$26.79	$28.72	$27.83	$24.40	$25.87	$27.90
FFS Physician Administered Drugs	$16.10	$13.61	$13.05	$14.29	$17.20	$15.66	$10.68	$12.58	$15.55	$17.09	$11.83	$10.63	$14.02
Encounter Physical Health Drugs	$66.72	$60.01	$64.06	$65.09	$61.52	$73.00	$63.06	$58.23	$61.20	$62.88	$60.69	$60.63	$63.09
Encounter Physician Administered Drugs	$17.44	$15.62	$17.32	$18.41	$16.87	$19.76	$15.80	$15.36	$17.08	$16.25	$16.09	$15.64	$16.80

Claim Counts	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Avg Monthly
Total Claim Count (FFS & Encounter)	1,105,849	1,007,517	1,080,076	1,114,155	1,042,654	1,144,164	984,041	991,912	1,050,307	1,058,691	1,038,520	1,055,991	1,056,156
Mental Health Carve-Out Drugs	167,909	154,155	164,637	169,930	157,817	177,133	164,968	164,360	172,366	174,577	171,729	173,516	167,758
FFS Physical Health Drugs	43,865	39,824	42,343	46,593	42,345	46,062	41,303	37,742	39,325	36,858	35,609	36,478	40,696
FFS Physician Administered Drugs	11,973	10,403	11,618	12,857	11,381	10,004	8,839	9,678	9,825	9,861	9,960	9,835	10,520
Encounter Physical Health Drugs	755,350	683,407	734,600	759,808	714,964	807,719	687,235	679,262	717,153	724,781	707,285	724,150	724,643
Encounter Physician Administered Drugs	126,752	119,728	126,878	124,967	116,147	103,246	81,696	100,870	111,638	112,614	113,937	112,012	112,540

Gross Amount Paid per Claim (Rebates not Subtracted)	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$79.97	$78.38	$78.76	$79.48	$80.03	$85.36	$86.86	$82.75	$84.54	$85.59	$84.78	$83.98	$82.54
Mental Health Carve-Out Drugs	$53.30	$52.71	$53.65	$54.81	$54.62	$53.80	$54.90	$53.45	$54.76	$54.25	$53.44	$53.25	$53.91
FFS Physical Health Drugs	$66.67	$64.64	$64.21	$66.82	$66.07	$66.48	$70.60	$66.97	$65.35	$69.48	$66.67	$68.13	$66.84
FFS Physician Administered Drugs	$126.24	$129.15	$112.26	$110.72	$149.99	$156.44	$131.70	$122.67	$141.62	$159.48	$115.61	$103.87	$129.98
Encounter Physical Health Drugs	$78.77	$77.70	$77.38	$76.64	$77.18	$81.37	$84.17	$81.06	$82.19	$84.42	$84.21	$83.35	$80.70
Encounter Physician Administered Drugs	$122.69	$115.49	$121.15	$131.77	$130.29	$172.30	$177.37	$143.96	$147.35	$140.44	$138.57	$139.04	$140.04

Gross Amount Paid per Claim - Generic-Multi Source Drugs (Rebates not Subtracted)	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Avg Monthly
Generic-Multi Source Drugs: Average Paid / Claim (FFS & Encounter)	$19.52	$18.87	$19.09	$19.51	$19.77	$20.11	$19.58	$19.20	$19.50	$20.35	$20.29	$20.60	$19.70
Mental Health Carve-Out Drugs	$17.52	$17.57	$17.69	$17.54	$17.51	$16.67	$16.78	$16.87	$16.95	$16.83	$16.80	$16.33	$17.09
FFS Physical Health Drugs	$21.40	$20.66	$20.14	$21.18	$19.84	$20.17	$21.00	$20.19	$19.92	$20.26	$20.60	$21.21	$20.55
Encounter Physical Health Drugs	$19.91	$19.11	$19.38	$19.90	$20.31	$20.94	$20.25	$19.77	$20.15	$21.29	$21.20	$21.71	$20.33

Gross Amount Paid per Claim - Branded-Single Source Drugs (Rebates not Subtracted)	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Avg Monthly
Branded-Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$459.18	$477.61	$487.07	$489.10	$497.17	$513.13	$547.92	$523.31	$542.78	$556.98	$550.47	$510.24	$512.91
Mental Health Carve-Out Drugs	$1,074.33	$1,059.38	$1,063.75	$1,103.08	$1,094.79	$1,104.69	$1,114.36	$1,103.23	$1,115.06	$1,108.05	$1,104.67	$1,101.10	$1,095.54
FFS Physical Health Drugs	$251.32	$252.25	$247.76	$262.76	$273.06	$265.24	$281.95	$265.58	$260.16	$279.80	$274.81	$271.28	$265.50
Encounter Physical Health Drugs	$442.99	$462.98	$473.21	$472.41	$480.02	$499.23	$534.38	$507.44	$528.00	$541.51	$534.05	$490.75	$497.25

Generic Drug Use Percentage	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Avg Monthly
Generic Drug Use Percentage	87.7%	88.3%	88.6%	88.7%	88.9%	88.7%	88.9%	88.9%	89.1%	89.2%	89.2%	88.4%	88.7%
Mental Health Carve-Out Drugs	96.6%	96.6%	96.6%	96.6%	96.6%	96.6%	96.5%	96.6%	96.6%	96.6%	96.6%	96.6%	96.6%
FFS Physical Health Drugs	80.3%	81.0%	80.6%	81.1%	81.7%	81.1%	81.0%	80.9%	81.1%	81.0%	81.9%	81.2%	81.1%
Encounter Physical Health Drugs	86.1%	86.8%	87.2%	87.5%	87.6%	87.4%	87.6%	87.4%	87.8%	87.9%	87.7%	86.9%	87.3%

Preferred Drug Use Percentage	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Sep-20	Avg Monthly
Preferred Drug Use Percentage	84.99%	85.38%	85.45%	85.16%	85.07%	85.15%	84.91%	84.80%	85.05%	85.39%	85.31%	86.79%	85.3%
Mental Health Carve-Out Drugs	73.31%	73.11%	73.04%	73.13%	73.07%	73.29%	73.16%	72.87%	73.05%	72.83%	72.84%	77.39%	73.4%
FFS Physical Health Drugs	94.57%	94.70%	94.96%	94.68%	94.30%	93.75%	89.26%	89.22%	89.01%	94.26%	94.25%	94.70%	93.1%
Encounter Physical Health Drugs	87.08%	87.64%	87.70%	87.29%	87.20%	87.26%	87.42%	87.39%	87.67%	87.94%	87.87%	88.65%	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 22, 2021

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

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	LATUDA	Antipsychotics, 2nd Gen	$6,665,360	16.0%	5,445	$1,224	Y
2	INVEGA SUSTENNA	Antipsychotics, Parenteral	$3,358,148	8.1%	1,590	$2,112	Y
3	VRAYLAR	Antipsychotics, 2nd Gen	$2,392,260	5.7%	2,125	$1,126	Y
4	INVEGA	Antipsychotics, 2nd Gen	$1,830,540	4.4%	1,449	$1,263	V
5	REXULTI	Antipsychotics, 2nd Gen	$1,755,220	4.2%	1,582	$1,109	V
6	ABILIFY MAINTENA	Antipsychotics, Parenteral	$1,741,662	4.2%	838	$2,078	Y
7	INVEGA TRINZA	Antipsychotics, Parenteral	$835,324	2.0%	129	$6,475	Y
8	STRATTERA*	ADHD Drugs	$734,079	1.8%	1,632	$450	Y
9	ARISTADA	Antipsychotics, Parenteral	$704,171	1.7%	311	$2,264	Y
10	BUPROPION XL	Antidepressants	$681,629	1.6%	35,122	$19	V
11	TRINTELLIX	Antidepressants	$670,903	1.6%	1,640	$409	V
12	SERTRALINE HCL	Antidepressants	$564,627	1.4%	55,016	$10	Y
13	VIIBRYD	Antidepressants	$535,794	1.3%	1,764	$304	V
14	DULOXETINE HCL	Antidepressants	$498,646	1.2%	34,599	$14	V
15	FLUOXETINE HCL	Antidepressants	$478,173	1.1%	39,933	$12	Y
16	TRAZODONE HCL	Antidepressants	$456,409	1.1%	45,403	$10	
17	ESCITALOPRAM OXALATE	Antidepressants	$358,481	0.9%	35,336	$10	Y
18	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	$313,125	0.8%	23,456	$13	
19	BIKTARVY	HIV	$308,018	0.7%	114	$2,702	Y
20	LAMOTRIGINE	Antiepileptics (non-injectable)	$289,237	0.7%	26,833	$11	Y
21	RISPERDAL CONSTA*	Antipsychotics, Parenteral	$286,312	0.7%	325	$881	Y
22	VENLAFAXINE HCL ER	Antidepressants	$254,946	0.6%	2,142	$119	V
23	SPRAVATO*	Antidepressants	$253,626	0.6%	235	$1,079	V
24	CHOLBAM*	Bile Therapy	$248,984	0.6%	6	$41,497	N
25	ASENAPINE MALEATE	Antipsychotics, 2nd Gen	$247,461	0.6%	446	$555	Y
26	LAMOTRIGINE ER	Antiepileptics (non-injectable)	$233,529	0.6%	2,583	$90	V
27	VENLAFAXINE HCL ER	Antidepressants	$219,530	0.5%	17,433	$13	Y
28	ARIPIPRAZOLE	Antipsychotics, 2nd Gen	$219,448	0.5%	17,634	$12	Y
29	QUETIAPINE FUMARATE*	Antipsychotics, 2nd Gen	$216,850	0.5%	18,748	$12	Y
30	AMITRIPTYLINE HCL*	Antidepressants	$209,990	0.5%	14,910	$14	Y
31	ATOMOXETINE HCL*	ADHD Drugs	$207,980	0.5%	3,706	$56	Y
32	Inj, Nusinersen, 0.1mg	Physican Administered Drug	$199,020	0.5%	1	$199,020	
33	CITALOPRAM HBR	Antidepressants	$189,488	0.5%	21,589	$9	Y
34	Inj Pembrolizumab	Physican Administered Drug	$187,055	0.4%	61	$3,066	
35	LANTUS SOLOSTAR*	Diabetes, Insulins	$172,257	0.4%	509	$338	Y
36	CONCERTA*	ADHD Drugs	$168,710	0.4%	536	$315	N
37	HUMIRA(CF) PEN*	Biologics for Autoimmune Conditions	$160,175	0.4%	47	$3,408	Y
38	MIRTAZAPINE	Antidepressants	$153,778	0.4%	10,529	$15	Y
39	WELLBUTRIN XL	Antidepressants	$150,968	0.4%	206	$733	V
40	OLANZAPINE	Antipsychotics, 2nd Gen	$150,746	0.4%	11,773	$13	Y
		Top 40 Aggregate:	**$29,302,662**		**437,736**	**$6,822**	
		All FFS Drugs Totals:	**$41,621,652**		**675,803**	**$635**	

*** Drug requires Prior Authorization**

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

Last updated: April 22, 2021

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

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	BIKTARVY	HIV	$308,018	3.1%	114	$2,702	Y
2	CHOLBAM*	Bile Therapy	$248,984	2.5%	6	$41,497	N
3	Inj, Nusinersen, 0.1mg	Physican Administered Drug	$199,020	2.0%	1	$199,020	
4	Inj Pembrolizumab	Physican Administered Drug	$187,055	1.9%	61	$3,066	
5	LANTUS SOLOSTAR*	Diabetes, Insulins	$172,257	1.7%	509	$338	Y
6	CONCERTA*	ADHD Drugs	$168,710	1.7%	536	$315	N
7	HUMIRA(CF) PEN*	Biologics for Autoimmune Conditions	$160,175	1.6%	47	$3,408	Y
8	TRIKAFTA*	Cystic Fibrosis	$135,073	1.4%	19	$7,109	N
9	SABRIL	Antiepileptics (non-injectable)	$126,143	1.3%	3	$42,048	N
10	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$124,996	1.3%	12	$10,416	Y
11	Etonogestrel Implant System	Physican Administered Drug	$123,657	1.2%	170	$727	
12	VYVANSE*	ADHD Drugs	$123,478	1.2%	725	$170	Y
13	ELIQUIS	Anticoagulants, Oral and SQ	$110,358	1.1%	301	$367	Y
14	VIMPAT	Antiepileptics (non-injectable)	$106,855	1.1%	240	$445	Y
15	STELARA*	Biologics for Autoimmune Conditions	$99,299	1.0%	16	$6,206	N
16	TRULICITY*	Diabetes, GLP-1 Receptor Agonists	$98,113	1.0%	184	$533	Y
17	Inj., Emicizumab-Kxwh 0.5 Mg	Physican Administered Drug	$93,539	0.9%	4	$23,385	
18	Aflibercept Injection	Physican Administered Drug	$93,224	0.9%	176	$530	
19	ALBUTEROL SULFATE HFA	Beta-Agonists, Inhaled Short-Acting	$88,321	0.9%	2,442	$36	Y
20	Epoetin Alfa, 100 Units Esrd	Physican Administered Drug	$84,628	0.8%	435	$195	
21	OPSUMIT*	Pulmonary Arterial Hypertension Oral and Inhale	$83,684	0.8%	8	$10,460	N
22	BUPRENORPHINE-NALOXONE*	Substance Use Disorders, Opioid & Alcohol	$82,973	0.8%	1,375	$60	Y
23	Mirena, 52 Mg	Physican Administered Drug	$79,418	0.8%	120	$662	
24	Injection, Pegfilgrastim 6mg	Physican Administered Drug	$79,197	0.8%	28	$2,828	
25	AFINITOR DISPERZ*	Antineoplastics, Newer	$77,620	0.8%	14	$5,544	
26	COSENTYX PEN (2 PENS)*	Biologics for Autoimmune Conditions	$74,498	0.7%	19	$3,921	N
27	SKYRIZI (2 SYRINGES) KIT*	Biologics for Autoimmune Conditions	$73,768	0.7%	4	$18,442	N
28	FLOVENT HFA	Corticosteroids, Inhaled	$69,766	0.7%	423	$165	Y
29	CIMZIA*	Biologics for Autoimmune Conditions	$69,323	0.7%	16	$4,333	N
30	LANTUS	Diabetes, Insulins	$69,290	0.7%	170	$408	Y
31	GENVOYA	HIV	$67,482	0.7%	28	$2,410	Y
32	Inj., Rituximab, 10 Mg	Physican Administered Drug	$65,018	0.7%	20	$3,251	
33	IBRANCE*	Antineoplastics, Newer	$64,786	0.6%	5	$12,957	
34	PULMOZYME	Cystic Fibrosis	$63,993	0.6%	42	$1,524	Y
35	CHANTIX*	Tobacco Smoking Cessation	$61,468	0.6%	144	$427	Y
36	DEMSER	STC 71 - Other Hypotensives	$61,017	0.6%	3	$20,339	
37	XULANE	STC 63 - Oral Contraceptives	$60,686	0.6%	357	$170	
38	ENBREL SURECLICK*	Biologics for Autoimmune Conditions	$59,575	0.6%	18	$3,310	Y
39	Injection, Ocrelizumab, 1 Mg	Physican Administered Drug	$59,115	0.6%	2	$29,558	
40	Inj. Pemetrexed Nos 10mg	Physican Administered Drug	$58,388	0.6%	42	$1,390	
		Top 40 Aggregate:	**$4,232,966**		**8,839**	**$11,617**	
		All FFS Drugs Totals:	**$9,997,146**		**123,063**	**$657**	

*** Drug requires Prior Authorization**

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

Last updated: April 22, 2021

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Drug Class Literature Scan: Colony Stimulating Factors

Date of Review: June 2021

Date of Last Review: January 2019
Literature Search: 09/01/18 – 03/25/21

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

Conclusions:

- There is limited new evidence available for evaluation of this class. No high-quality systematic reviews met inclusion criteria for review, many of which include biosimilar products not approved for use in the United States. One guideline was included in this review. Evidence supports previous recommendations with no compelling new evidence of efficacy or harms between granulocyte-colony stimulating factors (G-CSF), including between reference products and biosimilar formulations.
- Prophylaxis of febrile neutropenia (FN): evidence supports use with no differentiation between filgrastim, filgrastim biosimilars, tbo-filgrastim, pegfilgrastim, or pegfilgrastim biosimilars.[1]
- Treatment of FN: evidence supports use of filgrastim, filgrastim biosimilars, tbo-filgrastim, and sargramostim for FN due to chemotherapy; all reference and biosimilar G-CSF products and sargramostim (a granulocyte macrophage colony stimulating factor [GM-CSF]) are recommended for hematopoietic acute radiation syndrome (H-ARS).[1] (Note: Biosimilar products and tbo-filgrastim do not carry H-ARS as an official Food and Drug Administration (FDA) indication [**Appendix 6**]).
- Mobilization of Progenitor Cells:
    - Autologous Setting: evidence supports filgrastim, filgrastim biosimilars, and tbo-filgrastim; there is a lower rated recommendation for concurrent filgrastim or filgrastim biosimilars in combination with sargramostim.
    - Allogeneic Donors: evidence supports filgrastim and filgrastim biosimilars as the preferred choice, with tbo-filgrastim as an additional option.
    - Post-Hematopoietic Cell Transplant Supportive Care: evidence supports all G-CSF products.[1]
- Pegfilgrastim-apgf (Nyvepria™) was approved in June 2020 as a biosimilar to pegfilgrastim (Neulasta®) for all indications except H-ARS (**Appendix 6**).[2]
- Multiple new FDA safety alerts and package labeling changes have been enacted since the previous review (**Table 2**).

Recommendations:

- No changes to the Oregon Health Plan Preferred Drug List (PDL) based on clinical evidence.
- Evaluate comparative costs in executive session.

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Summary of Prior Reviews and Current Policy

- Most recent update of class occurred in January 2019, where tbo-filgrastim was reviewed and added as a preferred product. Currently all reference products are preferred on the PDL, while biosimilar products remain non-preferred. There are no class specific prior authorization criteria beyond preferred vs. non-preferred status.
- Previous evidence summaries concluded no compelling evidence of efficacy or harms differences between G-CSF products. Evidence is generally of moderate quality for FN prophylaxis, FN treatment, and hematopoietic progenitor cell transplant.
- Overall class usage is relatively low with fewer than 10 patients in the fee-for-service only population.

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, 11 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control, placebo-controlled, or non-FDA approved product included), or outcome studied (e.g., non-clinical).[3-13]

New Guidelines:

National Comprehensive Cancer Network-Myeloid Growth Factors

The NCCN issued updated guidelines in March of 2021 (version 2.2021) on the use of hematopoietic growth factors.[1] Methods for NCCN guideline development are published. Panel members with meaningful conflicts of interest (COI) are excluded from panel presentations, reviews, discussions, and voting in areas relevant to the COI. Active guidelines are reviewed and updated at least annually. NCCN categories for recommendations are based on level of clinical evidence and degree of consensus within the guideline panel related to both efficacy and safety. **(Table 1)** The level of evidence is based on quality of data, quantity of data, and consistency of data. This guideline review panel had fewer than half of the members with significant COI. These guidelines were developed specifically for adult patients. All recommendations are category 2A unless otherwise noted.

Table 1. NCCN Categories of Evidence and Consensus[1]

Category	Description
1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate

2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate
2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate
3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate
All recommendations are 2A unless otherwise indicated	

Febrile Neutropenia Prophylaxis

Use of G-CSF for prophylaxis of FN in patients with solid tumors and non-myeloid malignancies is stratified by risk. This risk is dependent on multiple factors including diagnosis, chemotherapy regimen, patient risk factors, and treatment goals. G-CSF are recommended in patients with high risk of FN (>20%) (category 1). Intermediate risk patients (10-20%) may be considered for G-CSF treatment with the presence of any risk factors (e.g. bone marrow involvement of tumor, recent surgery, liver dysfunction, etc). G-CSF prophylaxis is not recommended in those with low risk (<10%). Additionally, use of G-CSF should be considered in patients who develop febrile neutropenia or a dose limiting neutropenic event who did not receive G-CSF during the prior chemotherapy cycle. Filgrastim, tbo-filgrastim, and pegfilgrastim are all recommended (category 1), and FDA-approved biosimilars are considered appropriate substitutes for filgrastim and pegfilgrastim.[1]

Febrile Neutropenia Treatment

For a patient who develops FN, G-CSF use is dependent on previous exposure and agent used. Patients who received FN prophylaxis with a long acting product (e.g., pegfilgrastim or biosimilar) should not receive additional G-CSF. Pharmacokinetic data suggest it may not be beneficial to give additional G-CSF to a patient who received a long-acting product, though in prolonged neutropenia it may be considered. Patients who received prophylaxis with a short acting product (e.g., filgrastim or biosimilars, tbo-filgrastim) should continue therapy until absolute neutrophil count (ANC) recovery.[1]

Patients who develop FN, did not receive G-CSF prophylaxis, and do not have risk factors for an infection associated complication (e.g., sepsis syndrome, age greater than 65 years, ANC less than 100/mcL, neutropenia duration expected to be greater than 10 days, etc.) should not receive G-CSF or GM-CSF. Patients with risk factors may consider therapeutic use of short-acting G-CSF or GM-CSF until post-nadir ANC recovers to normal or near normal levels. Therapeutic use of G-CSF or GM-CSF should be used for radiation-induced myelosuppression following a radiologic or nuclear incident (H-ARS).[1]

Mobilization of Hematopoietic Progenitor Cells in Autologous Setting

Myeloid growth factors mobilization has multiple recommended regimens. Filgrastim (or biosimilars) or tbo-filgrastim administered via single or twice daily injections may be used as a single agent regimen. Use of these after combination chemotherapy, with the goal of mobilization during count recovery, may increase collection yields with fewer days of apheresis and reduce burden of residual tumor, but may also increase hospitalizations for neutropenic fever. Filgrastim (or biosimilars) plus sargramostim is an additional approach (category 2B). Filgrastim (or biosimilars) or tbo-filgrastim may also be combined with plerixafor for patients who do not mount a sufficient CD34+ count.[1]

Mobilization of Allogeneic Donors

Allogenic hematopoietic cell donors may receive either filgrastim (or biosimilars) or tbo-filgrastim (category 2B), with plerixafor (category 2B). For granulocyte transfusion, filgrastim (or biosimilars) or tbo-filgrastim (category 2B), as a single dose with dexamethasone, are recommended 8 to 24 hours prior to collection.[1]

Supportive Care Options
Filgrastim (or biosimilars) or tbo-filgrastim may be used for post-autologous hematopoietic cell transplant, haploidentical transplant, or cord blood transplant. Filgrastim is known to accelerate neutrophil recovery, though it has not been shown to impact survival. Additionally, pegfilgrastim (or biosimilars) can be considered for post-autologous hematopoietic cell transplant.[1]

After review, 3 guidelines were excluded due to poor quality or lack of applicability.[14-16]

New Formulations:
Pegfilgrastim-apgf (Nyvepria™) was approved in June 2020 as a biosimilar to pegfilgrastim (Neulasta®) and is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

New FDA Safety Alerts:

Table 2. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, Contraindications)	Addition or Change and Mitigation Principles (if applicable)
TBO-Filgrastim[17]	Granix®	Feb 2019	Warnings and Precautions	New subsection describing risk of alveolar hemorrhage. Hemoptysis resolved with discontinuation. Use for peripheral blood progenitor cell mobilization in healthy donors is not an approved indication.
Pegfilgrastim-jmdb[18]	Fulphila®	Mar 2019	Warnings and Precautions	Addition of aortitis Addition of nuclear imaging (hematopoietic activity is associated with transient positive bone imaging changes) Addition of thrombocytopenia Addition of myelodysplastic syndrome and acute myeloid leukemia in patients with breast and lung cancer
Filgrastim-sndz[19]	Zarxio®	Aug 2019	Warnings and Precautions	Addition of aortitis
Pegfilgrastim-bmez[20]	Ziextenzo®	Mar 2021	Warnings and Precautions	Addition of myelodysplastic syndrome and acute myeloid leukemia in patients with breast and lung cancer Addition of thrombocytopenia

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14. National Comprehensive Cancer Network. NCCN Hematopoietic Growth Factors: Short-Term Recommendations Specific to Issues with Covid-19 (SARS-CoV-2). https://www.nccn.org/covid-19/pdf/HGF_COVID-19.pdf Accessed March 29, 2021.
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17. Granix (tbo-filgrastim) Prescribing Information. Teva Pharmaceuticals. North Wales, PA. Mar 2019.
18. Fulphila (pegfilgrastim-jmdb) Prescribing Information. Mylan Pharmaceuticals. Morgantown, WV. Mar 2021.
19. Zarxio (filgrastim-sndz) Prescribing Information. Sandoz. Princeton, NJ. Aug 2019.
20. Ziextenzo (pegfilgrastim-bmez) Prescribing Information. Sandoz. Princeton, NJ. Mar 2021.

21. Waller CF, Ranganna GM, Pennella EJ, et al. Randomized phase 3 efficacy and safety trial of proposed pegfilgrastim biosimilar MYL-1401H in the prophylactic treatment of chemotherapy-induced neutropenia. *Annals of Hematology.* 2019;98(5):1217-1224.
22. Neupogen (filgrastim) Prescribing Information. Amgen, Inc. Thousand Oaks, Ca. Feb 2021.
23. Nivestym (filgrastim-aafi) Prescribing Information. Pfizer. Lake Forest, IL. Jul 2018.
24. Leukine (sargramostim) Prescribing Information. Sanofi. Bridgewater, NJ. Mar 2018.
25. Neulasta (pegfilgrastim) Prescribing Information. Amgen. Thousand Oaks, CA. Feb 2021.
26. Udenyca (pegfilgrastim-cbqv) Prescribing Information. Coherus Biosciences. Redwood City, CA. Sep 2019.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
filgrastim	NEUPOGEN	SYRINGE	IJ	Y
filgrastim	NEUPOGEN	VIAL	IJ	Y
pegfilgrastim	NEULASTA ONPRO	SYR W/ INJ	SQ	Y
pegfilgrastim	NEULASTA	SYRINGE	SQ	Y
sargramostim	LEUKINE	VIAL	IJ	Y
tbo-filgrastim	GRANIX	SYRINGE	SQ	Y
tbo-filgrastim	GRANIX	VIAL	SQ	Y
filgrastim-aafi	NIVESTYM	SYRINGE	SQ	N
filgrastim-aafi	NIVESTYM	VIAL	IJ	N
filgrastim-sndz	ZARXIO	SYRINGE	IJ	N
pegfilgrastim-apgf	NYVEPRIA	SYRINGE	SQ	N
pegfilgrastim-bmez	ZIEXTENZO	SYRINGE	SQ	N
pegfilgrastim-cbqv	UDENYCA	SYRINGE	SQ	N
pegfilgrastim-jmdb	FULPHILA	SYRINGE	SQ	N

Appendix 2: New Comparative Clinical Trials

A total of 61 citations were manually reviewed from the initial literature search. After further review, 60 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control, placebo-controlled, or non-US medication), or outcome studied (eg, non-clinical). The remaining trial is summarized in the table below. Full abstract is included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Waller et al.[21] Phase 3, MC, R, DB, PG, equivalence study Pharmacist preparing dose and clinician administering dose unblinded. Investigators and patients blinded.	1. MYL-1401H 6 mg (pegfilgrastim-jmdb, FULPHILA) 2. European Union-sourced reference pegfilgrastim 6 mg (NEULASTA) 2:1 randomization Received 24 hrs (+2 hr window) after end of chemo 6 planned chemo cycles every 3 weeks	Newly dx, ≥ 18 year old, Stage II/III breast Ca eligible to receive neoadjuvant/adjuvant TAC every 3 wks x 6 cycles N=194	CIN: Duration of severe neutropenia in cycle 1 (days with ANC < 0.5 x 10^9/L)	Mean (SD) 1. 1.2 days (0.93) 2. 1.2 days (1.0) MD -0.285 to 0.298 (within prespecified equivalence range with non-inferiority margin of 9%) Rates of TEAEs 1. 90% 2. 87% No deaths, treatment-related discontinuations, or suspected unexpected serious AE in either group.

Abbreviations: AE = adverse event; ANC = absolute neutrophil count; Ca = cancer; chemo = chemotherapy; CIN = chemotherapy induced neutropenia; DB = double-blind; Dx = diagnosed; hr = hour; MC = multicenter; MD = mean difference; PG = parallel-group; R= randomized; RCT = randomized clinical trial; SD = standard deviation; TAC = docetaxel/doxorubicin/cyclophosphamide; TEAE = treatment-emergent adverse events; wk = week.

Appendix 3: Abstracts of Comparative Clinical Trials

Waller, C. F., Ranganna, G. M., Pennella, E. J., Blakeley, C., Bronchud, M. H., Mattano, L. A., Jr., Berzoy, O., Voitko, N., Shparyk, Y., Lytvyn, I., Rusyn, A., Popov, V., Lang, I., Beckmann, K., Sharma, R., Baczkowski, M., Kothekar, M., Barve, A.

Randomized phase 3 efficacy and safety trial of proposed pegfilgrastim biosimilar MYL-1401H in the prophylactic treatment of chemotherapy-induced neutropenia

Pegfilgrastim is indicated for reducing the duration of neutropenia and incidence of febrile neutropenia in patients receiving cytotoxic chemotherapy. Here, safety and efficacy of MYL-1401H, a proposed pegfilgrastim biosimilar, were investigated as prophylaxis for chemotherapy-induced neutropenia. This was a phase 3, multicenter, randomized, double-blind, parallel-group equivalence trial of MYL-1401H vs European Union-sourced reference pegfilgrastim. Patients with newly diagnosed stage II/III breast cancer eligible to receive (neo) adjuvant chemotherapy with docetaxel/doxorubicin/cyclophosphamide every 3 weeks for 6 cycles were enrolled and randomized 2:1 to 6 mg of MYL-1401H or reference pegfilgrastim 24 h (+ 2-h window after the first 24 h) after the end of chemotherapy. The primary efficacy endpoint was the duration of severe neutropenia in cycle 1 (i.e., days with absolute neutrophil count (ANC) < 0.5 x 10⁹/L). Mean (standard deviation (SD)) duration of severe neutropenia in MYL-1401H and reference pegfilgrastim groups was 1.2 days (0.93) and 1.2 days (1.10), respectively. The 95% CI for least squares mean difference (- 0.285, 0.298) was within the predefined equivalence range of +/- 1 day. Secondary endpoints, including grade >= 3 neutropenia (frequency, 91% and 82% for MYL-1401H and reference pegfilgrastim, respectively), time to ANC nadir (mean (SD), 6.2 (0.98) and 6.3 (1.57) days), and duration of post-nadir recovery (mean (SD), 1.9 (0.85) and 1.7 (0.91) days) were comparable. Overall safety profiles of the study drugs were comparable. MYL-1401H demonstrated equivalent efficacy and similar safety to reference pegfilgrastim and may be an equivalent option for reducing incidence of neutropenia. (ClinicalTrials.gov , NCT02467868; EudraCT, 2014-002324-27).[21]

Appendix 4: Medline Search Strategy
Search performed 3/25/2021 Ovid

# ▲	Searches	Results
1	Filgrastim/ae, tu [Adverse Effects, Therapeutic Use]	259
2	pegfilgrastim.mp.	891
3	sargramostim.mp.	216
4	tbo-filgrastim.mp.	24
5	filgrastim-aafi.mp.	1
6	filgrastim-sndz.mp.	34
7	pegfilgrastim-apgf.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1
8	pegfilgrastim-bmez.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1
9	pegfilgrastim-cbqv.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	3
10	pegfilgrastim-jmdb.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	1252
12	limit 11 to (adaptive clinical trial or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	485
13	limit 12 to english language	477
14	limit 13 to yr="2018 -Current"	82

Appendix 5: Key Inclusion Criteria

Population	United States population
Intervention	G-CSF and GM-CSF in **Appendix 1**
Comparator	See **Appendix 1**
Outcomes	Symptom improvement, morbidity, mortality/survival, serious adverse events
Timing	Any study duration
Setting	Inpatient/outpatient combination or outpatient

Appendix 6: Summary of FDA labeled Indications of G-CSF and GM-CSF products

FDA Labeled Indications	Filgrastim NEUPOGEN[22]	Filgrastim-aafi NIVESTYM[23]	Filgrastim-sndz ZARXIO[19]	tbo-Filgrastim GRANIX[17]	Sargramostim LEUKINE*[24]
Decrease the **incidence** of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever.	x	x	x		
In adult and pediatric patients 1 month and older for reduction in the **duration** of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia.				x	
Reduce the time to neutrophil recovery and the **duration** of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML).	x	x	x		
To shorten time to neutrophil recovery and to reduce the **incidence** of severe and life-threatening infections and infections resulting in death following induction chemotherapy in adult patients 55 years and older with AML.					x
Reduce the **duration** of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT).	x	x	x		
For treatment of delayed neutrophil recovery or graft failure after autologous or allogeneic BMT in adult and pediatric patients 2 years of age and older.					x
For the acceleration of myeloid reconstitution following allogeneic BMT in adult and pediatric patients 2 years of age and older.					x

For the acceleration of myeloid reconstitution following autologous BMT or peripheral blood progenitor cell transplantation in adult and pediatric patients 2 years of age and older.					x
Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis.	x	x	x		
For the mobilization of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis and autologous transplantation in adult patients.					x
Reduce the incidence and duration of sequelae of severe neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia	x	x	x		
Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome)	x				x
	Pegfilgrastim NEULASTA†[25]	**Pegfilgrastim-apgf NYVEPRIA†[2]**	**Pegfilgrastim-bmez ZIEXTENZO†[20]**	**Pegfilgrastim-cbqv UDENYCA†[26]**	**Pegfilgrastim-jmdb FULPHILA†[18]**
Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically a significant incidence of febrile neutropenia.	x	x	x	x	X
Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).	x				

*Granulocyte Macrophage Colony Stimulating Factor (GM-CSF)

†Limitation of Use: NOT indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

Created: 3/31/2021

Drug Use Research & Management Program
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Prior Authorization Criteria Update: Oncology

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

Table 1. New oncology drugs

Generic Name	Brand Name
Dostarlimab-gxly	JEMPERLI
Idecabtagene vicleucel	ABECMA
Loncastuximab tesirine-lpyl	ZYNLONTA
Melphalan flufenamide	PEPAXTO
Tivozanib	FOTIVDA

Recommendation:

- Modify PA to include new, recently approved antineoplastic drugs.

Oncology Agents

Goal(s):

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

Length of Authorization:

- Up to 1 year

Requires PA:

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

Covered Alternatives:

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

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

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

Approval Criteria

9. All other diagnoses must be evaluated for evidence of clinical benefit.

   The prescriber must provide the following documentation:
   - medical literature or guidelines supporting use for the condition,
   - clinical chart notes documenting medical necessity, and
   - documented discussion with the patient about treatment goals, treatment prognosis and the side effects, and knowledge of the realistic expectations of treatment efficacy.

   RPh may use clinical judgement to approve drug for length of treatment or deny request based on documentation provided by prescriber. If new evidence is provided by the prescriber, please forward request to Oregon DMAP for consideration and potential modification of current PA criteria.

Table 1. Oncology agents which apply to this policy (Updated 05/03/2021)

New Antineoplastics are immediately subject to the policy and will be added to this table at the next P&T Meeting

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

Generic Name	Brand Name
cobimetinib fumarate	COTELLIC
copanlisib di-HCl	ALIQOPA
crizotinib	XALKORI
dabrafenib mesylate	TAFINLAR
dacomitinib	VIZIMPRO
daratumumab	DARZALEX
daratumumab/hyaluronidase-fihj	DARZALEX FASPRO
darolutamide	NUBEQA
decitabine and cedazuridine	INQOVI
degarelix acetate	FIRMAGON
dostarlimab-gxly	JEMPERLI
dinutuximab	UNITUXIN
durvalumab	IMFINZI
duvelisib	COPIKTRA
elotuzumab	EMPLICITI
enasidenib mesylate	IDHIFA
encorafenib	BRAFTOVI
enfortumab vedotin-ejfv	PADCEV
entrectinib	ROZLYTREK
enzalutamide	XTANDI
erdafitinib	BALVERSA
eribulin mesylate	HALAVEN
everolimus	AFINITOR
everolimus	AFINITOR DISPERZ
fam-trastuzumab deruxtecan-nxki	ENHERTU
fedratinib	INREBIC
gilteritinib	XOSPATA
glasdegib	DAURISMO
ibrutinib	IMBRUVICA
idecabtagene vicleucel	ABECMA
idelalisib	ZYDELIG
ingenol mebutate	PICATO

Generic Name	Brand Name
inotuzumab ozogamicin	BESPONSA
ipilimumab	YERVOY
Isatuximab	SARCLISA
ivosidenib	TIBSOVO
ixazomib citrate	NINLARO
larotrectinib	VITRAKVI
lenvatinib mesylate	LENVIMA
lisocabtagene maraleucel	BREYANZI
loncastuximab tesirine-lpyl	ZYNLONTA
lorlatinib	LORBRENA
lurbinectedin	ZEPZELCA
lutetium Lu 177 dotate	LUTATHERA
margetuximab-cmkb	MARGENZA
melphalan flufenamide	PEPAXTO
midostaurin	RYDAPT
moxetumomab pasudotox-tdfk	LUMOXITI
naxitamab-gqgk	DANYELZA
necitumumab	PORTRAZZA
neratinib maleate	NERLYNX
niraparib tosylate	ZEJULA
nivolumab	OPDIVO
obinutuzumab	GAZYVA
ofatumumab	ARZERRA
olaparib	LYNPARZA
olaratumab	LARTRUVO
olatuzumab vedotin-piiq	POLIVY
omacetaxine mepesuccinate	SYNRIBO
osimertinib mesylate	TAGRISSO
palbociclib	IBRANCE
panobinostat lactate	FARYDAK
pazopanib HCl	VOTRIENT
pembrolizumab	KEYTRUDA
pemigatinib	PEMAZYRE

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

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

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Prior Authorization Criteria Update: Orphan Drug

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

Table 1. New orphan drugs

Generic Name	Brand Name
Fosdenopterin	NULIBRY

Recommendation:

- Modify PA to include new, recently approved orphan drugs.

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
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. Indications for orphan drugs based on FDA labeling

Drug	Indication	Age	Dose	Recommended Monitoring
Burosumab-twza (CRYSVITA)	X-linked hypophosphatemia (XLH) FGF23-related hypophosphatemia in tumor-induced osteomalacia (TIO)	XLH ≥ 6 months TIO ≥ 2 years	Pediatric <18 years: Initial (administered SC every 2 weeks): XLH • <10 kg: 1mg/kg • ≥10 mg: 0.8 mg/kg TIO • 0.4 mg/kg Max dose of 2 mg/kg (not to exceed 90 mg for XLH or 180 for TIO) Adult: XLH 1 mg/kg monthly (rounded to nearest 10 mg; max 90 mg)	Baseline and Ongoing Monitoring • Use of active vitamin D **analogues** or oral phosphate within prior week; concurrent use is contraindicated • Fasting serum phosphorous: do not administer if serum phosphorous is within or above normal range • Renal function: use is contraindicated in ESRD or with severe renal impairment (CrCl <30 mL/min for adults or eGFR <30 mL/min/1.73m^2 for pediatric patients) • 25-hydroxy vitamin D levels: supplementation with vitamin D (cholecalciferol or ergocalciferol) is recommended as needed. Additional baseline monitoring for TIO only:

			TIO: 0.5 mg/kg monthly initially (Max 2 mg/kg or 180mg every 2 weeks)	• Documentation that tumor cannot be located or is unresectable • Elevated FGF-23 levels • Documentation indicating concurrent treatment for the underlying tumor is not planned (i.e., surgical or radiation)
Cerliponase alfa (BRINEURA)	To slow the loss of ambulation in symptomatic Batten Disease (late infantile neuronal ceroid lipofuscinosis type 2 or TPP1 deficiency)	3-17 years	300 mg every other week via intraventricular route	Baseline Monitoring • Enzymatic or genetic testing to confirm tripeptidyl peptidase 1 deficiency or CLN2 gene mutation • Baseline motor symptoms (e.g., ataxia, motor function, etc) • ECG in patients with a history of bradycardia, conduction disorders or structural heart disease Ongoing Monitoring • Disease stabilization or lack of decline in motor symptoms compared to natural history
Elapegademase-lvlr (REVCOVI)	adenosine deaminase severe combined immune deficiency (ADA-SCID)	N/A	Initial: 0.2mg/kg twice weekly; No max dose	Baseline Monitoring • CBC or platelet count Ongoing Monitoring • trough plasma ADA activity • trough erythrocyte dAXP levels (twice yearly) • total lymphocyte counts
Fosdenopterin (NULIBRY)	To reduce risk of mortality in patients with molybdenum cofactor deficiency (MoCD) Type A	N/A	Dosed once daily; Preterm Neonate (Gestational Age <37 weeks) Initial: 0.4 mg/kg Month 1: 0.7 mg/kg Month 3: 0.9 mg/kg Term Neonate (Gestational Age ≥ 37 weeks)	Initiation of therapy is recommended with known or presumed MoCD Type A. Discontinue therapy if diagnosis is not confirmed with genetic testing.

			Initial: 0.55 mg/kg Month 1: 0.75 mg/kg Month 3: 0.9 mg/kg Age ≥ 1 year 0.9 mg/kg	
Givosiran (GIVLAARI)	acute hepatic porphyria	≥ 18 years	2.5 mg/kg monthly	Baseline and ongoing monitoring • Liver function tests
Lonafarnib (ZOKINVY)	To reduce risk of mortality in Hutchinson-Gilford Progeria Syndrome For treatment of processing-deficient Progeroid Laminopathies with either: ○ Heterozygous LMNA mutation with progerin-like protein accumulation ○ Homozygous or compound heterozygous ZMPSTE24 mutations	≥12 months AND ≥0.39 m^2 body surface area	• Initial 115 mg/m^2 twice daily • Increase to 150 mg/m^2 twice daily after 4 months Round all doses to nearest 25 mg	Baseline and ongoing monitoring • Contraindicated with strong or moderate CYP3A inducers, midazolam, lovastatin, simvastatin, or atorvastatin • Comprehensive metabolic panel • CBC • Ophthalmological evaluation • Blood pressure • Pregnancy test (if childbearing potential)
Lumasiran (OXLUMO)	Treatment of primary hyperoxaluria type 1 to lower urinary oxalate levels	Adult and pediatric patients	**<10 kg** Loading: 6 mg/kg once/month for 3 doses Maintenance: 3 mg/kg once/month **10 kg to <20 kg** Loading: 6 mg/kg once/month for 3 doses Maintenance: 6 mg/kg once every 3 months	

			≥ 20 kg Loading: 3 mg/kg once/month for 3 doses Maintenance: 3 mg/kg once every 3 months All maintenance dosing begins 1 month after last loading dose.	
Luspatercept (REBLOZYL)	Anemia (Hg <11 g/dL) due to beta thalassemia in patients requiring regular red blood cell transfusions Anemia (Hg <11 g/dL) due to myelodysplastic syndromes with ring sideroblasts or myelodysplastic/ myeloproliferative neoplasm with ring sideroblasts and thrombocytosis	≥ 18 years	Initial: 1 mg/kg subcutaneously Max dose of 1.25 mg/kg every 3 weeks for beta thalassemia Max dose of 1.75 mg/kg every 3 weeks for myelodysplastic syndromes	Baseline Monitoring/Documentation • 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 • Trial and failure of an erythropoiesis stimulating agent in patients with myelodysplastic syndromes • Hemoglobin level • Blood pressure Ongoing Monitoring • Discontinue if there is not a decrease in transfusion burden after 3 maximal doses (about 9-15 weeks) • Hemoglobin level • Blood pressure

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

Approval Criteria		
2. Is the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Is the request for a drug FDA-approved for the indication, age, and dose as defined in **Table 1**?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.
4. Is the request for continuation of therapy in a patient previously approved by FFS?	**Yes:** Go to **Renewal Criteria**	**No:** 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?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is this medication therapy being prescribed by, or in consultation with, an appropriate medical specialist?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Have other therapies been tried and failed?	**Yes:** Approve for up to 3 months (or length of treatment) whichever is less Document therapies which have been previously tried	**No:** 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?	**Yes:** Go to #2	**No:** Go to #3
2. Has the adverse event been reported to the FDA Adverse Event Reporting System?	**Yes:** Go to #3 Document provider attestation	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
3. Is baseline efficacy monitoring available?	**Yes:** Go to #4	**No:** Go to #5
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?	**Yes:** Approve for up to 6 months Document benefit	**No:** 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)?	**Yes**: Approve for up to 6 months Document benefit and provider attestation	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 6/21(SF); 2/21 (SF); 8/20 (SS); 6/20; 2/20
Implementation: TBD; 3/1/21; 11/1/20; 9/1/20; 7/1/20

ProDUR Report for January through March 2021
High Level Summary by DUR Alert

DUR Alert	Example	Disposition	# Alerts	# Overrides	# Cancellations	# Non-Response	% of all DUR Alerts	% Overridden
DA (Drug/Allergy Interaction)	Amoxicillin billed and Penicillin allergy on patient profile	Set alert/Pay claim	7	1	0	6	0.01%	**14.3%**
DC (Drug/Inferred Disease Interaction)	Quetiapine billed and condition on file for Congenital Long QT Sundrome	Set alert/Pay claim	2,371	470	0	1,901	1.86%	**19.8%**
DD (Drug/Drug Interaction)	Linezolid being billed and patient is on an SNRI	Set alert/Pay claim	2,452	663	0	1,789	1.69%	**27.0%**
ER (Early Refill)	Previously filled 30 day supply and trying to refill after 20 days (80% = 24 days)	Set alert/Deny claim	85,823	14,920	21	70,879	67.37%	**17.4%**
ID (Ingredient Duplication)	Oxycodone IR 15mg billed and patient had Oxycodone 40mg ER filled in past month	Set alert/Pay claim	26,601	6,424	2	20,171	20.91%	**24.1%**
LD (Low Dose)	Divalproex 500mg ER billed for 250mg daily (#15 tabs for 30 day supply)	Set alert/Pay claim	824	128	0	696	0.60%	**15.5%**
LR (Late Refill/Underutilization)	Previously filled for 30 days supply and refill being billed 40 days later.	Set alert/Pay claim	5	4	0	1	0.01%	**80.0%**
MC (Drug/Disease Interaction)	Bupropion being billed and patient has a seizure disorder	Set alert/Pay claim	861	215	0	646	0.62%	**25.0%**
MX (Maximum Duration of Therapy)		Set alert/Pay claim	486	130	2	354	0.37%	**26.7%**
PG (Pregnancy/Drug Interaction)	Accutane billed and client has recent diagnosis history of pregnancy	Set alert/Deny claim	17	12	0	5	0.01%	**70.6%**
TD (Therapeutic Duplication)	Diazepam being billed and patient recently filled an Alprazolam claim.	Set alert/Pay claim	8,249	2,152	0	6,096	6.48%	**26.1%**
		Totals	**127,696**	**25,119**	**25**	**102,544**	**99.91%**	**19.7%**

ProDUR Report for January through March 2021

Top Drugs in Enforced DUR Alerts

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Remeron (Mirtazapine)	1,630	247	1,383	14,081	11.6%	15.2%
ER	Lorazepam	355	84	271	13,358	2.7%	23.7%
ER	Alprazolam	186	38	108	8,081	2.3%	20.4%
ER	Diazepam	113	28	85	4,645	2.4%	24.8%
ER	Buspirone (Buspar)	3,075	473	2,602	31,758	9.7%	15.4%
ER	Lamictal (Lamotrigine)	5,236	933	4,303	41,870	12.5%	17.8%
ER	Seroquel (Quetiapine)	4,162	882	3,280	30,988	13.4%	21.2%
ER	Zyprexa (Olanzapine)	2,335	475	1,860	18,879	12.4%	20.3%
ER	Risperdal (Risperidone)	1,862	344	1,518	13,508	13.8%	18.5%
ER	Abilify (Aripiprazole)	3,264	532	2,732	26,246	12.4%	16.3%
ER	Wellbutrin (Bupropion)	5,993	917	5,076	67,076	8.9%	15.3%
ER	Hydrocodone/APAP	9	0	8	907	1.0%	0.0%
ER	Oxycodone	17	3	13	1,526	1.1%	17.6%
ER	Suboxone (Buprenorphine/Naloxone)	71	15	56	1,852	3.8%	21.1%
ER	Zoloft (Sertraline)	7,479	1,337	6,141	74,174	10.1%	17.9%
ER	Prozac (Fluoxetine)	5,060	760	4,300	52,346	9.7%	15.0%
ER	Lexapro (Escitalopram)	4,520	661	3,859	46,635	9.7%	14.6%
ER	Celexa (Citalopram)	2,296	294	1,999	26,871	8.5%	12.8%
ER	Trazodone	6,456	1,068	5,388	59,301	10.9%	16.5%
ER	Cymbalta (Duloxetine)	4,313	648	3,665	44,706	9.6%	15.0%
ER	Intuniv (Guanfacine)	1,729	186	1,163	12,273	14.1%	10.8%

ProDUR Report for January through March 2021
Early Refill Reason Codes

DUR Alert	Month	# Overrides	CC-3 Vacation Supply	CC-4 Lost Rx	CC-5 Therapy Change	CC-6 Starter Dose	CC-7 Medically Necessary	CC-13 Emergency Disaster	CC-14 LTC Leave of Absence	CC-Other
ER	January	4,050	89	298	989	2	2,296	228	0	148
ER	February	3,027	64	207	746	3	1,713	154	0	140
ER	March	3,978	108	265	936	8	2,273	217	0	171
	Total =	**11,055**	**261**	**770**	**2,671**	**13**	**6,282**	**599**	**0**	**459**
	Percentage of total overrides =		**2.4%**	**7.0%**	**24.2%**	**0.1%**	**56.8%**	**5.4%**	**0.0%**	**4.2%**

ProDUR Report for January through March 2021

High Level Summary for Drug-Drug

DUR Alert	Month	# Alerts	# Overrides	# Cancellations	# Non-Response
DD (Drug/Drug Interaction)	January	71	17	0	54
DD (Drug/Drug Interaction)	February	57	5	0	52
DD (Drug/Drug Interaction)	March	2,324	641	0	1,683
DD (Drug/Drug Interaction)	**1Q2021 Total =**	**2,452**	**663**	**0**	**1,789**

March 2021 Drug-Drug Alerts by Therapeutic Category

Therapeutic Category	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Clims Screened
ANTI-ANXIETY - BENZODIAZEPINES	87	51	36	9,758	0.89%
ANTICONVULSANTS	278	87	191	22,633	1.23%
ANTIPSYCHOTIC,ATYPICAL,DOPAMINE,SEROTONIN ANTAGNS	625	195	430	31,025	2.01%
ANTIPSYCHOTICS, ATYP, D2 PARTIAL AGONIST/5HT	37	12	25	10,737	0.34%
ANTIPSYCHOTICS,DOPAMINE ANTAGONISTS,BUTYROPHENONE	56	22	34	1,151	4.87%
ANTIPSYCHOTICS,PHENOTHIAZINES	40	18	22	1,118	3.58%
BIPOLAR DISORDER DRUGS	42	6	36	3,967	1.06%
NOREPINEPHRINE AND DOPAMINE REUPTAKE INHIB	54	5	49	24,217	0.22%
OPIOID ANALGESIC AND NON-SALICYLATE ANALGESICS	10	9	1	639	1.56%
OPIOID ANALGESICS	11	5	6	614	1.79%
SELECTIVE SEROTONIN REUPTAKE INHIBITOR	537	117	420	76,691	0.70%
SEROTONIN-2 ANTAGONIST/REUPTAKE INHIBITORS	236	46	190	20,937	1.13%
TRICYCLIC ANTIDEPRESSANTS,REL.NON-SEL.REUPT-INHIB	126	22	104	11,139	1.13%
TX FOR ATTENTION DEFICIT-HYPERACT.(ADHD)	46	10	36	3,974	1.16%
March Total =	**2,185**	**605**	**1,580**	**218,600**	**1.00%**

SUPPORT ACT and ProDUR:

CMS has issued new Federal legislation for States to prospectively monitor opioids and CNS depressants, specifically benzodiazepines and antipsychotics based on requirements of the Substance Use Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act (SUPPORT Act).

FDB ProDUR provides the files in 3 sections for Drug-Drug Interactions:
Severity Level 1: SL1s- MAJOR interaction.
Severity Level 2: SL2s- SEVERE Interaction.
Severity Level 3: SL3s- MODERATE Interaction

OR: SL1 (Major only) until February 2021. Now includes all SL2 and SL3

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

Severity Level 2, "Severe Interaction"
Interactions that produce serious consequences in most patients. However, monitoring and/or titrating the agent(s) involved in severe interactions can significantly minimize the risk of adverse effects. If a drug product's label contains the phrase, "concurrent use should be avoided," the interaction is assigned this severity level.

Severity Level 3, "Moderate Interaction"
Interactions of moderate severity. The clinician should assess the patient's characteristics and take action as needed.

In response to the FDA Drug Safety Communication of August 31, 2016, requiring strong warnings for opioids and CNS Depressants (such as olanzapine, an antipsychotic) when used in combination, the following SL3 monographs were added to DDIM:

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

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Retro-DUR Intervention History by Quarter FFY 2020 - 2021

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Change Form	Desvenlafaxine Salt Formulations	Unique Prescribers Identified		52	28	
		Unique Patients Identified		53	28	
		Total Faxes Successfully Sent		44	19	
		Prescriptions Changed to Recommended Within 6 Months of Intervention		20	6	
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention		$11,528	$2,380	
	Fluoxetine Tabs to Caps	Unique Prescribers Identified	23			
		Unique Patients Identified	23			
		Total Faxes Successfully Sent	15			
		Prescriptions Changed to Recommended Within 6 Months of Intervention	7			
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$578			
	Venlafaxine Tabs to Caps	Unique Prescribers Identified	146	293	128	
		Unique Patients Identified	147	300	132	
		Total Faxes Successfully Sent	99	210	76	
		Prescriptions Changed to Recommended Within 6 Months of Intervention	84	120	33	
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$66,886	$52,265	$9,414	

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Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Cost Savings	RetroDUR Dose Consolidation	Total Claims Identified	51	50	44	
		Total Faxes Successfully Sent	10	17	6	
		Prescriptions Changed to Recommended Dose Within 3 Months of Fax Sent	4	9		
		Prescriptions Changed to Alternative Dose Within 3 Months of Fax Sent	11	1		
		Prescriptions Unchanged after 3 Months of Fax Sent	28	7		
		Safety Monitoring Profiles Identified	7	10	1	
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Faxes Sent	($5,218)	$7,724	$0	

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Expert Consultation Referral	Antipsychotic Use in Children	Total patients identified	936	606	586	
		Profiles sent for expert review	13	6	7	
		Prescribers successfully notified	13	6	4	
		Patients with change in antipsychotic drug in following 90 days	2			
		Patients with continued antipsychotic therapy in the following 90 days	8	6	4	
		Patients with discontinuation of antipsychotic therapy in the following 90 days	2			

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Non-Adherence	Antipsychotics in people w/schizophrenia	Total patients identified	69	66	28	
		Total prescribers identified	68	66	28	
		Prescribers successfully notified	68	66	25	
		Patients with claims for the same antipsychotic within the next 90 days	37	36	7	
		Patients with claims for a different antipsychotic within the next 90 days	5	4		

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

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Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Safety Net	Antipsychotic Dose Consolidation	Total patients identified		62	50	
		Patients with a paid claim for the drug (based on HSN) within 14 days		37	26	
		Patients without a paid claim within 14 days		25	6	
	Combination Opioid-Sedative	Total patients identified	120	123	75	
		Total prescribers identified	119	123	75	
		Prescribers successfully notified	112	110	56	
		Patients with discontinuation of therapy within next 90 days	29	26	31	
		Patients with new prescription for naloxone within next 90 days	4	4	2	
		Average number of sedative drugs dispensed within next 90 days	24	23	7	
		Average number of sedative prescribers writing prescriptions in next 90 days	24	23	7	
	ICS/LABA	Disqualified	6	6	6	
		Disqualified - Erroneous denial	6	6	6	
		Faxes Sent	1	2		
		Fax Sent - Combination Inhaler	1	1		
		No Subsequent Pulmonary Claims		1		
	Oncology Denials	Total patients identified	1	3		
		Total prescribers identified	1	3		
		Prescribers successfully notified	1	1		
		Patients with claims for the same drug within the next 90 days	1	2		
		Patients with claims for any oncology agent within the next 90 days	1	2		

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Retro-DUR Intervention History by Quarter FFY 2020 - 2021

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
	TCAs in Children	Total patients identified	10	6	8	
		Total prescribers identified	10	6	8	
		Prescribers successfully notified	7	1	5	
		Patients with claims for a TCA within the next 90 days	2	1		
		Patients with claims for an alternate drug (SSRI, migraine prevention, or diabetic neuropathy) within the next 90 days		1		

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COVID-19 Viral Testing

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SARS coronavirus 2 (SARS-CoV-2), more commonly known as coronavirus disease (COVID-19), has impacted the people of Oregon with over 36,000 total cases and over 600 deaths reported as of October 2020.[1] Testing for this virus is critical for case identification to slow the disease spread and ensure infected persons are triaged to receive appropriate patient care. Fortunately, testing for COVID-19 has become more accessible for individuals as the COVID-19 pandemic has persisted. However, confusion still exists for many patients and practitioners regarding COVID-19 testing recommendations. The focus of this newsletter is to clarify who should be tested, timing of tests and where to receive the COVID-19 test in Oregon.

COVID-19 Testing Approval

The Oregon Health Authority (OHA) recommends using only tests that have emergency use authorization (EUA) from the U.S. Food and Drug Administration (FDA). On February 4th, 2020 the Department of Health and Human Services issued an EUA under the Public Readiness and Emergency Preparedness Act (PREP). This EUA allows for unapproved medical products or unapproved uses of approved medical products to be used in an emergency to diagnose, treat, or prevent serious disease, in this case COVID-19.[2] Technologies and therapies under EUA have not undergone full FDA scrutiny and these authorizations are not FDA-approvals. Likely, once the COVID-19 pandemic is declared over, the EUA will expire as seen in the EUA expiration of peramivir in 2010 after the 2009 H1N1 influenza pandemic.[3] Additionally, the EUA could be revoked if deemed appropriate by the FDA.

Types of COVID-19 Tests

Three types of tests are available for COVID-19: viral tests (e.g., molecular based and antigen tests) and serologic (antibody) tests. A viral tests tells individuals if they have a current infection with COVID-19, while an antibody test might tell individuals if they have had a past infection.[4] Antibody testing is occurring at certain locations around Oregon, however, the OHA states there is insufficient evidence to suggest that antibody tests are a reliable indicator that an individual has or had COVID-19 or that they have immunity.[5] Therefore, COVID-19 testing referenced in the remainder of this article will refer to viral testing, as there is uncertainty with antibody testing.

Viral tests can be conducted via one of two technologies: a molecular test or an antigen test.[6] Molecular tests detect viral ribonucleic acid (RNA) via reverse transcription polymerase chain reaction (RT-PCR) process and is considered the gold standard. The second method is rapid antigen testing which detects the presence of the nucleocapsid protein antigen. Both test detect active viral COVID-19 infection. Viral testing using RT-PCR provides results in less than an hour to more than 2 days.[4] Rapid antigen tests take approximately 15 minutes but are less sensitive than molecular assays. Rapid antigen testing is most accurate in the early stages of infection, when there is higher viral loads. Rapid antigen testing may require confirmation with RT-PCR within 2 days as a confirmatory test.[6] Both of these tests, antigen and molecular, can be conducted as either a point-of-care (POC) test or lab processed test.[7]

Accuracy of the testing methods is determined by sensitivity and specificity. The *sensitivity* of a test refers to the ability of the test to correctly identify those with a disease compared with *specificity*, which allows a test to identify those patients without disease. A recent Cochrane review found the average sensitivity of the antigen tests to be 56.2% (95% confidence interval [CI], 29.5% to 79.8%) with an average specificity of 99.5% (95% CI, 98.1% to 99.9%).[8] Sensitivity for the molecular assay test was higher with an average sensitivity of 95.2% (95% CI, 86.7% to 98.3%) and specificity of 98.9% (95% CI, 97.3% to 99.5%).[8] The evidence was found to be at high risk of bias with an emphasis on the need for additional trials.

Testing Collection Methods

It is recommended that nasopharyngeal, mid-turbinate (MT) or nasal swabs be utilized for testing versus other testing collection methods. Accuracy of recommended collection sites range from 75% to 95% and are displayed in **Table 1.**[6] Oral tests were 56% sensitive and saliva tests were 85% sensitive (and inconsistent); therefore, these testing sites are currently not preferred.[6] Collection by the patient or healthcare worker was deemed appropriate for nasal and MT testing. Due to the quality of studies available, the certainty of the evidence is very low.

Table 1. Accuracy of COVID-19 Results based on Collection Site*[6]

	Nasal	Nasopharyngeal	Mid-turbinate
Sensitivity (95% CI)	76% (59% to 94%)	97% (92% to 100%)	100% (93% to 100%)
Specificity (95% CI)	100% (99% to 100%)	100% (99% to 100%)	100% (99% to 100%)

Key: * Bases on estimates of positive and negative test results in a hypothetical population of 1000 individuals

Timing of Testing

Close contacts of confirmed or presumptive COVID-19 cases are recommended to be tested 3-14 days after exposure, although the optimal time for testing remains unknown.[9] Recommendations for the timing of testing for other populations are as follows:[6]

- Symptomatic individuals: tested as soon as possible.
- Patients undergoing surgery: ideally 48-72 hours before surgery.
- Patients undergoing immunosuppressive procedures: ideally 48-72 hours before procedure.

If suspicion is low for COVID-19 the Infectious Diseases Society of America (IDSA) recommends not repeating the test if results are negative; however, the test should be repeated in light of a negative test result if the patient is hospitalized or at high suspicion of having COVID-19.[6] Repeat testing should take place within 24-48 hours of a negative test result if an individual is an appropriate candidate for repeat testing.[6] If a patient tests positive, there is no need to retest for at least 3 months.[6]

Recommendations for Who Should be Tested

OHA published updates in October for COVID-19 recommendations relating to viral testing for individuals with symptoms (**Table 2**) and without symptoms (**Table 3**).[9] Additional guidance on who should receive testing if resources are limited is available on the OHA website.[9] Per the Centers for Disease Control and Prevention (CDC), COVID-19 symptoms may appear 2-14 days after exposure to the virus.[10] Additionally, OHA recently recommends that close contacts of confirmed or presumptive COVID-19 cases, people exposed to COVID-19 in a congregate setting, and migrant/seasonal agricultural workers upon arrival in Oregon be tested for COVID-19 regardless of whether they have symptoms or not.[9] Clinicians may order commercial tests based on their clinical judgement.

Table 2. OHA Recommendations for COVID-19 viral testing for any person with new onset of a COVID-19 –like illness which includes, but not limited to:[9]

- **Fever or chills**
- **Shortness of breath or difficulty breathing**
- **Headache**
- **New loss of taste or smell**
- **Congestion or runny nose**
- **Cough**
- **Fatigue**
- **Muscle or body aches**
- **Sore throat**
- **Nausea or vomiting**
- **Diarrhea**

Table 3. OHA Recommendations for COVID-19 viral testing for people without symptoms of a COVID-19-like illness limited to the following groups:[9]

- **People who identify as Black, African-American, Latino, Latina, Latino, American Indian/Alaska Native, Asian, Asian American or Pacific Islander**
- **People who identify as having a disability**
- **People whose first language is not English**

COVID-19 Testing is available to all Oregon Health Plan (OHP) members at no cost[12]

Interpreting COVID-19 Test Results to Patients

OHA has provided messaging for providers to utilize with patients regarding the accuracy of COVID-19 viral tests and antibody tests (**Figure 1 and Figure 2**).[9] Patients should be considered non-contagious if it has been at least 10 days since symptom onset and fever free for at least 24 hours. If a patient has been in close contact with someone with COVID-19 and tests negative, they should still self-isolate for at least 14 days.[11]

Figure 1. Test Results and Accuracy Limitations - messaging for patients *with* symptoms of COVID-19[9]

Messaging to patients with symptoms of COVID-19		
	Viral test	**Antibody test**
Positive	You have COVID-19. Protect your community by isolating according to public health recommendations.	Approximately half of test results may be falsely positive.* Even if you do have antibodies, it's not yet known whether they provide protection against reinfection.
Negative	Tests are falsely negative in about 30% of patients with symptoms. Assume that you have COVID-19 and protect your community by isolating until you feel better.	Your symptoms may be caused by an illness that is not COVID-19. Results may also be falsely negative even if you have or had COVID-19. Antibody tests may not become positive for weeks following infection.

Figure 2. Test Results and Accuracy Limitations - messaging for patients *without* symptoms of COVID-19[9]

Messaging to patients without symptoms of COVID-19		
	Viral test	**Antibody test**
Positive	You have COVID-19. You may or may not develop symptoms. Protect your community by isolating according to public health recommendations.	Approximately half of test results may be falsely positive.* Even if you do have antibodies, it's not yet known whether they provide protection against reinfection.
Negative	You may have COVID-19. Tests may be falsely negative, and a negative result provides no indication that you are protected from infection.	Results may be falsely negative even if you have or had COVID-19. Antibody tests may not become positive for weeks following infection.

* False positive rate depends on the specificity of the test used and the prevalence of COVID-19 in the community.

Where to Direct Individuals for Testing

OHA recommends individuals contact their primary healthcare provider or clinic if they believe they need testing. For individuals without a doctor, OHA has a phone number, 211,

that will provide individuals with help for finding nearby clinics that test for COVID-19.[12] Additionally, the OHA website has a COVID-19 test site finder map that individuals can utilize by submitting their address, ZIP code, or city and a list of nearby COVID-19 testing sites will populate.[13] Sites listed include clinics, urgent care sites, and pharmacies that test for COVID-19. Providers and other individuals can contribute to the map by submitting a new location that tests for COVID-19 on the interactive map. New locations are reviewed and the map is usually updated within 12 hours with the new location.[13] Additionally, patients may be directed to their respective county website which lists COVID-19 testing sites in their region.

Oregon COVID-19 Testing Sites can be found at: https://govstatus.egov.com/or-oha-covid-19-testing

For testing sites in Oregon, the majority require appointments to be made ahead of time. This may prove to be difficult for patients who are not established with a primary care provider, do not have a phone, or do not have internet access to schedule an appointment. Two organizations that are currently accepting individuals for COVID-19 testing with no appointment required are:[14,15]
Oregon Health and Science University (OHSU): https://www.ohsu.edu/health/coronavirus-resources#section-1117926
Virginia Garcia Medical Center (select events): https://virginiagarcia.org/coronavirus/

Pharmacy Testing Sites

Some of the most convenient locations for patients to receive COVID-19 testing include pharmacies. Rite Aid and Walgreens have COVID-19 testing sites provided at no cost. Rite Aid currently has 17 locations and Walgreens has 2 locations performing COVID-19 tests in Oregon.[16,17] Safeway and Albertsons are also offering testing at pharmacies but for an approximate cost of $140 each.
Rite Aid: https://www.riteaid.com/pharmacy/services/covid-19-testing.
Walgreens: https://www.walgreens.com/findcare/covid19/testing

Patients can access testing by completing a screening survey online to determine eligibility, receive an appointment for testing, have the test performed by the patient or pharmacist using a nasal swab, and have test results relayed back to the patient via email or phone call.[16,17]

The Role of the Provider

Information regarding COVID-19 testing changes rapidly. In order to provide accurate information and minimize confusion, it is paramount that providers stay up to date on information regarding COVID-19 testing. Providers and patients can utilize reliable sources of information for COVID-19 testing, such as, the OHA and CDC. In this way, accurate and optimal patient care can be provided to the individuals of Oregon.

Additional information on Coronavirus Management can be found at https://pharmacy.oregonstate.edu/drug-policy/newsletters/coronavirus-management

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2019-2020 Food and Drug Administration Drug Safety Communications Update

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One of the key roles of the Food and Drug Administration (FDA) is to monitor medication safety. The FDA collects post-marketing adverse effects of medications and issues Drug Safety Communications when necessary.[1] In the past two years, sixteen drug safety communications have been released. This article will focus on recent warnings for medications more commonly used in the primary care setting, namely montelukast, gabapentinoids, febuxostat, and benzodiazepines. **Table 1** highlights the most relevant aspects of the warnings, followed by a presentation of additional related evidence.

Table 1. Summary of 2019-2020 FDA Drug Safety Communications

Drug Safety Communication	Summary of Evidence	Risk Mitigation Strategies
Montelukast		
Potential risk of serious neuropsychiatric side effects such as suicidal ideation, aggressiveness, and anxiety with montelukast use	Causal relationship inconclusive due to poor quality of evidence	• Use ICS and ICS/LABA for asthma • Use antihistamines for allergic rhinitis
Pregabalin, Gabapentin		
Increased risk of respiratory depression (including risk of death) with concomitant use of gabapentinoids with other CNS depressing medications (including opioids and benzodiazepines)	Increased risk with concomitant CNS depressants likely based on retrospective cohort and case-control analyses	• Avoid co-prescribing of gabapentinoids with other CNS depressants (especially opioids and benzodiazepines) • Initiate pregabalin at low dose (25 mg 1-3 times daily) and up-titrate slowly • Initiate gabapentin at low dose (100 mg 1-3 times daily) and up-titrate slowly
Febuxostat		
Increased risk of cardiovascular and all-cause mortality from use of febuxostat in gout treatment	Increased risk of cardiovascular and all-cause mortality likely from secondary endpoints from CARES trial	• Use renally adjusted allopurinol for chronic urate lowering therapy • Only use febuxostat in those with contraindications to allopurinol
Benzodiazepines		
Increased risk for abuse, addiction, physical dependence, and withdrawal even when used at recommended doses	Increased risk likely (especially when used concurrently with opioids) based on systematic reviews	• Avoid prescribing benzodiazepines for greater than 2-4 weeks in duration • Initiate at low dose • Prescribe only 1-2 week supplies at a time • Avoid alprazolam if possible • Use a discontinuation taper for patients on therapy for at least 2-4 weeks

Abbreviations: CARES - Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities; CNS – central nervous system; ICS – inhaled corticosteroid; LABA – long acting beta agonist

Montelukast:

Montelukast, a leukotriene receptor antagonist, is approved for asthma, prevention of exercise induced bronchoconstriction, and allergic rhinitis.[2] The FDA published a Drug Safety Communication in March 2020 detailing the risk of serious neuropsychiatric (NP) side effects, including suicidal ideation (SI), irritability, and anxiety associated with montelukast use.[3] This risk was escalated to a Black Box Warning (BBW) due to new data indicating an increased risk of SI. A total of 82 suicide cases associated with montelukast use were identified from the FDA Adverse Event Reporting System (FAERS) database, 34 of which contained sufficient data to support montelukast precipitating the suicidal event. However, since many of these 34 cases had additional risk factors for SI, a causal relationship with montelukast could not be established.[3]

A systematic review from 2018 assessed montelukast's relationship with NP side effects. Four of the included studies showed no statistically significant increase in SI following montelukast use. One nested case-control study included in this systematic review noted that the odds ratio (OR) for SI was not statistically significant at 0.70 (95% confidence interval [CI] 0.36-1.39 for *all* ages assessed [ages 5-24 years]). However, the sub-cohort of people aged 19-24 years had an OR of 5.15 (95% CI 1.16-22.86), which was statistically significant.[4] Two additional retrospective studies (one cohort and one case-control) published after the systematic review demonstrated a statistically significant increase in the risk of NP side effects in asthmatic patients 18 years or younger after montelukast exposure. One showed a relative risk (RR) of 12.0 (95% CI 1.6-90.2),[5] and the other showed an OR of 1.91 (95% CI 1.15-3.18).[6]

The evidence for increased NP side effects from montelukast is inconclusive due to the poor quality of evidence (mostly retrospective studies with potential confounders). However, safer alternatives are available for all approved indications of montelukast. Thus, the FDA drug safety communication recommends use of an inhaled corticosteroid (ICS), ICS/long-acting beta-agonist (LABA), or an as needed ICS/LABA for asthma[7] and antihistamines for allergic rhinitis[8] as first-line therapy, especially in patients with pre-existing mental health conditions such as anxiety and previous SI. If montelukast is used, patients should be warned about the possible risk of NP side effects such as increased anxiety, irritability, and sleep disturbances.

Gabapentinoids (Gabapentin and Pregabalin):

Gabapentin and pregabalin are gamma aminobutyric acid (GABA) analogs approved for partial onset seizures and post-herpetic neuralgia.[9,10] Pregabalin is also approved for diabetic peripheral neuropathy and fibromyalgia.[10,11] The FDA published a Drug Safety Communication in December 2019 detailing an increased risk of respiratory depression in patients with respiratory risk factors, including concurrent use of other central nervous system (CNS) depressants (such as opioids and benzodiazepines), elderly patients, and patients with chronic obstructive pulmonary disease (COPD).[12] The FDA identified 49 case reports of patients experiencing respiratory depression following gabapentinoid administration. Of the cases, 92% of patients had pre-existing loss of lung function or concurrent use of another CNS depressant; 12 of these patients died (all of whom had at least one additional risk factor for respiratory depression in addition to gabapentinoid use). An analysis of which patients had pre-existing loss of lung function, concurrent CNS depressant medication use, or both was not provided. The risk in healthy individuals is less supported.[12] Additional evidence related to the FDA warnings for gabapentinoids is displayed in **Table 2**.

Table 2. Evidence Supporting Risk with Gabapentinoids

Type of Study	RF for RD in the study	Outcomes	Results
Population-based, nested, case-control[13] N = 5875 Ages: 15-105 years	Concurrent opioid use Chronic lung disease (23% of all patients)	Opioid related death following exposure to concomitant gabapentin	Gabapentin + opioid vs. opioid alone OR = 1.49; 95% CI 1.18-1.88
Retrospective, cohort[14] N = 44,152 (gabapentin), 736,835 (opioid), 15,343 (both) Ages: 16-64 years	Concurrent opioid use (2% of all patients)	Risk of IPH or ED visit for RD	When compared to *regular use gabapentin: Gabapentin alone with **sustained overuse: OR = 0.9; 95% CI 0.4-1.7 Concurrent gabapentin + opioid, 1 medication with **sustained overuse: OR = 2.6; 95% CI 2.0-3.5 Concurrent gabapentin + opioid, both medications with **sustained overuse: OR = 4.1; 95% CI 1.8-9.6
*Regular Use: Gabapentin ≤3600 mg/day; opioid ≤50 MME/day **Sustained Overuse: Gabapentin >3600 mg/day; opioid >50 MME/day AND ≥3 rolling calendar quarters at these doses			
Abbreviations: CI – confidence interval; ED – emergency department; IPH – inpatient hospitalization; MME – morphine milligram equivalents; OR – odds ratio; RF – risk factors; RD – respiratory depression			

Based upon the evidence and the increased utilization of gabapentinoids in recent years,[12] providers should be mindful of the increased risk for respiratory depression with gabapentin and pregabalin use, especially when prescribed concurrently with opioids or other CNS depressants. The risk for respiratory depression in elderly patients or patients with compromised lung function (i.e., COPD, obesity, and obstructive sleep apnea) is less clear as there are currently no studies that have specifically assessed these risk factors. If gabapentinoids are used, they should be initiated at a low dose (see **Table 1**) and up-titrated slowly to the minimum effective dose for each patient. Patients should be closely monitored for confusion/disorientation, extreme sleepiness or lethargy, and slowed, shallow, or difficult breathing.

Febuxostat:

In February 2019, the FDA released a Drug Safety Communication about the increased risk of cardiovascular (CV) death from febuxostat, a xanthine oxidase inhibitor.[15,16] The FDA mandated that the labeling include a BBW and updated the indication to "hyperuricemia in adult patients with gout who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable."[16] Data from the Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES) trial, as outlined in **Table 3**, primarily led to this Drug Safety Communication.[16]

Table 3. Evidence Supporting Risk with Febuxostat

Type of Study	Outcomes	Results
Multicenter, double-blind, non-inferiority (for primary endpoint), superiority (for secondary endpoints)[17] N = 6190 Ages: greater than 18 years	Primary: 4-point MACE (CV death, nonfatal MI, nonfatal stroke, unstable angina with urgent revascularization) Secondary: Death from any cause, death from CV cause	Primary: Febuxostat vs. allopurinol: HR = 1.03; 95% CI 0.87-1.23 Secondary: Death any cause: HR = 1.22; 95% CI 1.01-1.47 Death CV cause: HR = 1.34; 95% CI 1.03-1.73
Abbreviations: CI – confidence interval; CV – cardiovascular; HR – hazard ratio; MACE – major adverse cardiovascular event; MI – myocardial infarction		

Although the data for increased risk of CV death and all-cause mortality with febuxostat is based on secondary endpoints alone, the severity of the risk cannot be ignored. Providers should utilize allopurinol as first-line therapy in patients with gout, especially in patients with pre-existing CV disease or at high CV risk. Febuxostat should generally be reserved for patients whom have contraindications to allopurinol (such as hypersensitivity reactions including Stevens-Johnson Syndrome and Allopurinol Hypersensitivity Syndrome). If used,

the FDA recommends that patients prescribed febuxostat be advised to seek emergency medical attention if they experience any of the following: chest pain, shortness of breath, rapid or irregular heart rate, unilateral numbness, dizziness, trouble speaking, or a sudden and severe headache.[16]

Benzodiazepines:

Benzodiazepines (BZDs) bind to post-synaptic GABA-A receptors in the brain, leading to hyperpolarization of neurons and less neuronal firing.[11] This action leads to the anxiolytic, anticonvulsant, and CNS depressive properties of BZDs. The FDA published a Drug Safety Communication in September 2020 detailing an increased risk of abuse, addiction, physical dependence, and withdrawal with BZD use, even when used at recommended doses.[18] The BBW was expanded on the label to reflect this information. From a review of published literature and emerging case reports, the FDA found new information that reinforced the knowledge that BZDs were widely prescribed in the United States (US) and often for longer durations than recommended. In 2018 for example, 50% of patients who were prescribed a BZD received prescriptions for greater than 2 months. In 2019, 92 million BZD prescriptions were dispensed to patients in an outpatient setting, the most common of which were for alprazolam, clonazepam, and lorazepam. The FDA also reviewed 104 cases from the FAERS database detailing abuse, dependence, or withdrawal from BZD monotherapy at recommended doses. Of the cases, 80% of patients described withdrawal symptoms following cessation of the BZD, even when tapered.[18] Additional evidence related to the FDA warnings for BZDs is displayed in **Table 4**.

Table 4. Evidence Supporting Risk with Benzodiazepines

Type of Study	Outcomes	Results
2019 Systematic, epidemiologic review[19] Ages: 12 years and older	Epidemiological findings	• 1 in 20 patients prescribed a BZD • Deaths related to BZD OD increased by 400% from 1996 to 2015 • 2.2% of patients misused BZD, 64% of whom obtained BZD from friend or family • Alprazolam most commonly misused BZD (73% of all misuse)
Systematic review[20] N = 353,658 Ages: 20 years and older	Risk of falls, traffic accidents, and injuries from those accidents for new BZD use vs. non-use	Risk of falls: OR = 2.8; 95% CI, 2.2-3.6 Traffic accidents: OR = 3.4; 95% CI, 1.7-6.8 Injuries from traffic accidents: OR = 3.1; 95% CI, 1.5-6.2
Systematic review[20] N = 14,117 Ages: 18 years and older	Mortality following BZD use	OR = 1.4; 95% CI, 1.1-1.7
Abbreviations: BZD – benzodiazepine; CI = confidence interval; OD – overdose; OR = odds ratio		

For most indications, including generalized anxiety disorder (GAD), BZDs are generally recommended as second or third-line options.[21] First-line options will vary by disease state, but for GAD, selective serotonin reuptake inhibitors are recommended first-line.[21] Based upon the evidence, BZDs should be avoided unless there are no other alternatives available. Alprazolam in particular should be avoided if possible. Alprazolam has an increased risk of misuse, abuse, and withdrawal due to its rapid absorption, low lipophilicity, and short half-life as compared to other BZDs.[22] If BZDs are used, they should be prescribed at the lowest starting dose and for a short amount of time (less than 2-4 weeks). Prescribing limited quantities (i.e., no more than 1-2 weeks at a time) may help to limit misuse.[23] Unfortunately, evidence demonstrating what duration of BZD therapy warrants discontinuation via taper are lacking. However, most guidance statements and guidelines recommend that a taper over *at least* 8-10 weeks be considered for patients prescribed BZDs for at least 2-4 weeks.[23-25] In general, avoiding abrupt discontinuation may be best for all patients on BZDs to avoid severe withdrawal symptoms.

Conclusion

Staying up to date on serious adverse effects of medications is an important responsibility for healthcare providers. Based on this review, montelukast may be associated with serious NP side effects (such as SI) and should generally be reserved as second-line therapy for both asthma and allergic rhinitis. Gabapentin and pregabalin may increase the risk of serious respiratory depression when co-prescribed with opioids (and other CNS depressants such as benzodiazepines), and thus opioid or BZD co-prescribing should be avoided as much as possible. Febuxostat appears to increase the risk of all-cause and CV related mortality, and it should generally be reserved for patients that cannot tolerate allopurinol. Due to increased risk of abuse, physical dependence and withdrawal, BZDs should be reserved for second or third-line therapy. Long-term BZD use should generally be avoided due to an increased risk of morbidity and mortality. If utilized, they should be prescribed at a low dose in limited quantities for less than 2-4 weeks. Pharmacists and other healthcare providers should strive to remain up to date on the ever-changing information about medications to ensure the safety of their patients. Providers should always consider submitting a medication adverse event report to the FAERS database via FDA MedWatch (https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program) to ensure that unexpected outcomes are incorporated, trended, and investigated, if necessary.[26,27]

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Coronavirus Disease-2019 Vaccine Update

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The need to rapidly develop a vaccine that inhibits Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection and the resulting Coronavirus Disease-2019 (COVID-19) has stimulated significant scientific innovation.[1] In May 2020, the United States (U.S.) Department of Health and Human Services launched Operation Warp Speed, a partnership between government and industry, with the goal of delivering 300 million doses of a safe and effective vaccine by January 2021.[2] An unapproved vaccine may receive Emergency Use Authorization (EUA) status by the Food and Drug Administration (FDA) during a public health emergency when there are no adequate, approved and available alternatives.[3] To receive EUA status, the developers must demonstrate clear and compelling efficacy and safety in a large, well-designed, phase 3 clinical trial. The issuance of an EUA is different than an FDA approval of a vaccine.[3] The FDA expects manufacturers whose COVID-19 vaccines are authorized under an EUA to continue their clinical trials to obtain additional safety and efficacy information and pursue approval.[3] This newsletter will focus on the vaccine candidates currently under development or authorized for emergency use in the U.S. to reduce infection associated with SARS-CoV-2.

Challenges in Vaccine Development

Over 200 COVID-19 vaccine candidates are under development worldwide.[4] Vaccine development targeting the SARS-CoV-2 virus poses several challenges.[1] Most of the SARS-CoV-2 vaccine candidates target the receptor-binding domain of the surface spike protein of the coronavirus. The spike protein latches on to cells and unlocks them for virus entry; an antibody that binds to the spike and prevents the virus from getting into cells should stop the virus from causing infection.[5] Although the coronavirus' spike protein is a promising method to develop immunity, optimizing antigen design to ensure at least 50% efficacy in placebo-controlled trials has been challenging.[1] As with naturally acquired infection, the potential duration of immunity is unknown; similarly, whether single-dose vaccines will confer immunity is uncertain.[1] For novel vaccines, large-scale manufacturing has never been done, so facilities capable of producing large quantities of product must be identified, technologies transferred, and manufacturing processes adapted, all without knowing if the vaccine candidate is viable.[1] Finally, in a high-mortality situation, populations may not accept randomized, controlled trials with placebo groups; although other approaches that address such concerns may be scientifically feasible, they're not as fast, and the results can be harder to interpret.[6]

Messenger RNA Vaccines

Vaccines with the greatest potential for rapid development are RNA-based platforms.[1] Two COVID-19 vaccines (**Table 1**) with FDA EUA as of December 17, 2020 are messenger RNA (mRNA) vaccines. mRNA vaccines can be made quickly because they use a synthetic process and do not require culture or fermentation.[1] To date, there are no mRNA vaccines for any infectious diseases except COVID-19. RNA vaccines function on the premise that mRNA coded for pathogen antigen can be delivered into human cells and result in production of antigen within the cell.[2] Unlike other vaccines, this triggers an immune response without the introduction of live, killed, or subunit portions of the virus.[2] The mRNA cannot cause infection, does not alter human DNA, and is broken down by normal processes in human cells. One of the main concerns of utilizing mRNA-based platforms is the potential of synthetically formulated mRNA to cause a severe adverse reaction due to its inherent inflammatory nature.[4] In addition, mRNA is highly susceptible to extracellular ribonucleases and is rapidly degraded, so it must be encapsulated in a protective lipid system to facilitate delivery into human cells.[2] Because mRNA is naturally unstable, it must be stored frozen below -20 °C, which complicates the shipping, storage, and administration of mRNA vaccines.[5] Some companies are working on stabilizing the molecule at higher temperatures by freeze-drying the vaccine.[5]

Viral Vector Vaccines

Two SARS-CoV-2 vaccines under development use non-replicating viral vectors to transport recombinant SARS-CoV-2 spike protein genes into the human cell (**Table 1**).[2] The infected cells display the coronavirus spike protein on their surfaces, which stimulates the immune system to develop antibodies.[5] This transient viral DNA protein is not incorporated into the host cell DNA. Clinical use of this strategy has been used in Middle East Respiratory Syndrome (MERS), Zika, and Ebola vaccines.[4] The Astra-Zeneca vaccine uses a simian adenovirus and the Janssen/Johnson & Johnson vaccine uses a human adenovirus.[2] Because these adenoviruses do not replicate, a high dose is required, producing about 12 hours of flu-like symptoms as the immune system responds to the vaccine.[5] The Janssen/Johnson & Johnson vaccine was administered as a single dose in the first phase 3 trial. A second phase 3 trial is using 2 doses of the vaccine to evaluate safety and efficacy.

Recombinant Protein-Based Vaccines

The Novavax and Sanofi/GlaxoSmithKline (GSK) immunizations include SARS-CoV-2 proteins, but no genetic material (**Table 1**). Since this method is actually producing a unique protein, it is harder to manufacture than other vaccines and requires more time to ensure production meets high -quality standards. The proteins are recognized by T-cells as target antigens, which generate an immune response. The Novavax product has shown efficacy in initial trials. The Sanofi/GSK vaccine has not produced the desired level of response in subjects over the age of 50 years. A different formulation will begin a phase 2 trial in early 2021. The most promising COVID-19 vaccine candidates developed through Operation Warp Speed are described in **Table 1.**

Table 1. COVID-19 Vaccine Candidates[7]

Vaccine	How Supplied	Schedule	Storage and Dilution Requirements
mRNA Vaccines			
Pfizer-BioNTech (BNT162b2) Comirnaty® (tozinameran) Approved for ≥16 yo under FDA EUA	5 doses (30 mcg) in 2.25 mL MDV PF powder	0.3 mL IM for 2 doses (Days 0, 21)	▪ Frozen in ultra-cold storage between -80°C to -60°C (-112°F to -76°F) for 6 months. ▪ Once thawed, store refrigerated 2°C to 8°C (36°F to 46°F) for up to 5 days. ▪ Once reconstituted, store vials between 2°C to 25°C (35°F to 77°F) and use within 6 hours of dilution.
Moderna (mRNA-1273) Approved for ≥18 yo under FDA EUA	10 doses (100 mcg) in 6.3 mL MDV PF suspension	0.5mL IM for 2 doses (Days 0, 28)	▪ Frozen between -25°C to -15°C (-13°F to 5°F) for 6 months. ▪ Refrigerated between 2°C to 8°C (36F to 46°F) for 30 days. ▪ Room temperature between 8°C to 25°C (46°F to 77°F) for up to 12 hours. ▪ Once punctured, contents of vial must be administered within 6 hours.
Viral Vector Vaccines			
AstraZeneca-Oxford* (AZD1222)	10 doses in MDV	2 doses (Days 0, 28)	▪ Refrigerated between 2°C to 8°C for up to 3 months.
Janssen/Johnson & Johnson* (Ad26.COV2-S)*	5 doses in MDV	1 dose	▪ Frozen at -20°C for 2 years ▪ Refrigerated between 2°C to 8°C (36°F to 46°F) for up to 3 months.
Recombinant Protein Vaccines			
Novavax (NVX-CoV2373)*	N/A	2 doses (Days 0, 21)	▪ Refrigerated between 2°- 8°C (36 to 46°F) for up to 3 months.
Sanofi/ GlaxoSmithKline*	N/A	2 doses (Days 0, 21)	N/A

Abbreviations: EUA=Emergency Use Authorization; FDA=Food and Drug Administration; IM=intramuscular; MDV= Multi-dose Vial; mL=milliliters; mRNA=messenger RNA; N/A=Not Available; mcg=micrograms; PF= Preservative Free; yo=Years Old
Key: * Approved age range not yet determined

Efficacy of the BioNTech/Pfizer Vaccine (BNT162b2)

Evidence from one phase 1 randomized controlled trial (RCT)[8] and one combined Phase 2/3 (RCT)[9] was evaluated by the FDA for EUA of the Pfizer 30 mcg vaccine. The placebo-controlled, phase 2/3 RCT was conducted at 152 worldwide sites in healthy adults aged 16 years and older (n=43,448).[9] One hundred thirty clinical trial sites were based in the U.S.[9] Subjects with stable chronic conditions including human immunodeficiency virus (HIV), hepatitis B virus or hepatitis C virus infections were eligible for trial participation.[9] However, subjects diagnosed with an immunocompromising condition, treated with immunosuppressive therapy, or with a history of COVID-19 were excluded from the trial.[9] Pregnant or breast feeding women and people with a history of severe adverse reaction associated with vaccine and/or severe allergic reaction (i.e. anaphylaxis) to any component of the vaccine were also excluded from this study.[9]

At the safety cutoff date, 37,706 participants had a median of 2 months of safety data available after the second dose.[9] Of these 37,706 participants, 49% were female, 83% were White, 28% were Hispanic, 9% were Black, 4% were Asian, and 21% had at least one coexisting condition.[9] The median age was 52 years, and 42% of participants were older than 55 years of age.[9] Among 36,523 subjects with no evidence of prior SARS-CoV-2, there were 8 cases of COVID-19 with onset at least 7 days after the second dose of vaccine among vaccine recipients compared with 162 cases in the placebo arm.[9] High-quality evidence from this trial showed this vaccine was 95% effective in preventing symptomatic COVID-19 compared to placebo (Relative Risk [RR] 0.05, 95% Confidence Interval [CI] 90.3 to 97.6%).[10]

Efficacy of the Moderna Vaccine (mRNA-127)

The phase 3 RCT evaluating the 2-dose Moderna 100 mcg vaccine randomized 30,418 subjects 1:1 to either vaccine or placebo in people 18 years of age and older at 99 U.S. clinical sites.[11] Inclusion and exclusion criteria were similar to the Pfizer study except for the range of included ages. Among study participants, 47% were female, 79% were White, 21% were Hispanic, 10% were Black, and 5% were Asian.[11] The mean age was 52 years and 25% were 65 years of age and older.[11] The median length of follow-up after the second dose was 7 weeks, though ongoing analysis is planned for all patients for 24 months.[11] The vaccine was 94.1% effective (95% CI 89.3 to 96.8) in preventing COVID-19 disease at least 14 days after the second vaccine dose with 11 cases of COVID-19 in the vaccine group and 185 in the placebo group.[11] At the time of the analysis of these 196 COVID-19 cases, none in the vaccine group and 30 in the placebo group were classified as severe.[11]

Safety Data with mRNA Vaccines

Depending on vaccine product, age group, and vaccine dose, approximately 80–89% of vaccinated persons develop at least one local symptom and 55–83% develop at least one systemic symptom following vaccination **(Table 2).**[12] Most systemic post-vaccination symptoms are mild to moderate in severity, occur within the first three days of vaccination, and resolve within 1–3 days of onset.[12] The rate of adverse reactions reported with mRNA vaccines is similar to rates observed with the zoster vaccine.[11] These symptoms are more frequent and severe following the second dose and among younger persons compared to older persons.[12] Antipyretic or analgesic medications (e.g., acetaminophen, non-steroidal anti-inflammatory drugs) may be taken for the treatment of post-vaccination local or systemic symptoms, if medically appropriate. However, routine prophylactic administration of these medications for the purpose of preventing post-vaccination symptoms is not currently recommended, as information on the impact of such use on mRNA COVID-19 vaccine-induced antibody responses is not available at this time.[12] A 2014 systematic review assessed the evidence for a relationship between prophylactic antipyretic administration and antibody response in children.[13] Though prophylactic antipyretic administration led to relief of the local and systemic symptoms after primary vaccinations, there was a reduction in antibody responses to some vaccine antigens.[13]

Hypersensitivity-related adverse events were observed in 0.63% of Pfizer and 1.5% of Moderna COVID-19 vaccine clinical trial participants who received the vaccine, compared to 0.51% and 1.1%, respectively, in the placebo groups.[12] Anaphylaxis following vaccination was not observed in the mRNA vaccine clinical trials.[12] However, anaphylactic reactions have been reported following receipt of the Pfizer COVID-19 vaccine during vaccination outside of clinical trials.[12] People who experience anaphylaxis with the first vaccine dose (i.e. they were hospitalized, they needed to use an EpiPen), should not receive a second dose.[12] Unless persons develop a contraindication to vaccination, they should be encouraged to complete the series even if they develop local or systemic symptoms following the first dose to optimize protection against COVID-19.[12] Protection from the vaccine is not immediate and 1-2 weeks is required following the second dose to be considered fully vaccinated.[12] Limited data are currently available regarding the efficacy of a single dose. Patients should be counseled on the importance of completing the two-dose series to optimize protection.[12] The vaccines are not interchangeable and both doses of the series should be completed with the same product.[12] Common and serious adverse effects observed up to 8 weeks after vaccination with the mRNA vaccines are outlined in **Table 2.**

Table 2. COVID-19 mRNA Vaccine Safety[12]

Vaccine	Common Adverse Effects	Serious Adverse Effects
Pfizer-BioNTech (BNT162b2)	Injection Site Pain (84%) Fatigue (63%) Headache (55%) Muscle Pain (38%) Chills (32%) Joint Pain (24%) Fever (14%)	▪ SAEs: 0.0% to 4.6% ▪ More frequent after second dose ▪ Fewer SAEs if >56 yo (≤2.8%) vs. ≤55 yo (≤4.6%)
Moderna (mRNA-1273)	Injection Site Pain (92%) Fatigue (69%) Headache (63%) Muscle Pain (60%) Joint Pain (45%) Chills (43%)	▪ SAEs: 1% to 4.8% ▪ More frequent after second dose ▪ Fewer SAEs if ≥ 65 yo
Abbreviations: NR= Not Reported; SAEs = Severe Adverse Effects; yo = Years Old		

Vaccine Safety Reporting Methods

To continuously monitor the safety of the new COVID-19 vaccines, the FDA and CDC are collaborating on safety surveillance using existing vaccine safety monitoring infrastructure, including the Vaccine Adverse Event Reporting System (VAERS), Vaccine Safety Datalink, and Clinical Immunization Safety Assessment Project. Adverse events that occur in a recipient following COVID-19 vaccination should be reported to VAERS. Reporting is encouraged for any other clinically significant adverse event even if it is uncertain whether the vaccine caused the event.[12] Information on how to submit a report to VAERS is available at https://vaers.hhs.gov or by calling 1-800-822-7967.

In addition, CDC has developed a new, voluntary smartphone-based tool, V-SAFE, which is an after-vaccination health checker for people who receive COVID-19 vaccines. V-SAFE will use text messaging and web surveys from CDC to check in with vaccine recipients for health problems following COVID-19 vaccination. The system also will provide telephone follow up to anyone who reports medically significant adverse events. Reports to V-SAFE indicating a medically significant health impact, including pregnancy, are followed up by the CDC/V-SAFE call center to collect additional information to complete a VAERS report, if appropriate.[12]

Pearls for Patient Education

- RNA vaccine technology is new, but not unknown, as RNA vaccines have been studied for more than a decade for influenza and rabies.[14]
- Vaccine trials were large studies, with over 30,000 volunteers of various ages, races, and underlying diseases.[14]

- COVID-19 mRNA vaccines have been rigorously tested for safety before being authorized for use in the U.S. in large clinical trials and data review by the FDA.[14]
- RNA vaccines do not impact human DNA or genetic makeup. Human cells use mRNA every day to make many types of life sustaining proteins.[14]
- RNA vaccines do not enter the cell nucleus. They are not live vaccines and do not carry a risk of causing disease in the vaccinated person.[14]

COVID-19 Resources

- The CDC provides Interim Clinical Considerations for the administration of mRNA COVID-19 vaccines.
- Additional health provider resources for COVID-19 vaccine patient education can be accessed at the CDC Website.
- Vaccine information and a Providers Communication Toolkit are available at the OHA COVID-19 Healthcare Partner Resources page.
- The OHA has also developed resources in Spanish at the Vacnunacovid page.

Conclusions

Two new COVID-19 mRNA vaccines received EUA by the FDA in late December 2020. The need for rapid development of vaccines to provide worldwide protection from the SARS-CoV-2 virus necessitated combined phase 2 and 3 clinical trials to expedite safety and efficacy assessments for these novel products. Initial data shows over 94% efficacy for both vaccines, and collection of long-term data is ongoing. Both vaccines are safe with expected mild to moderate symptoms (injection site pain, fever, headache, myalgia) lasting 1 to 3 days post immunization. At this time, data are not available to determine how long the mRNA vaccines will provide protection, nor is there evidence that these vaccines prevent transmission of SARS-CoV-2 from person to person.[3] Additional vaccines using 2 different platforms, viral vector and recombinant proteins, are currently in phase 3 trials with results expected in early 2021.

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Prospective Safety Edit Policy Proposal: Antipsychotics In Young Children

Policy Proposal:

Evidence for use of antipsychotics in children was recently evaluated by the Pharmacy and Therapeutics Committee.[1] Utilization data indicates that a small proportion of children less than 6 years of age are prescribed antipsychotics (66 patients in 2020). Because evidence regarding the use of antipsychotics in children is limited, recommendations were made by the Pharmacy and Therapeutics Committee in April 2021 to implement safety edits to ensure appropriate use of antipsychotics in children.

Antipsychotics can be associated with significant risk of long-term adverse events. Few antipsychotics have been studied in young children, and efficacy and safety has not been established for any antipsychotic in young children less than 5 years of age. Indications with the most evidence of effectiveness in children include use for irritability associated with autistic disorder (including symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods). Both risperidone and aripiprazole have an indication for irritability associated with autism for patients at least 5 and 6 years of age, respectively.[2,3] Common indications and FDA-approved ages for other antipsychotics include use for bipolar disorder or schizophrenia in adolescents, but none have an FDA-approved indication for these conditions in young children. Current guidelines recommend non-pharmacological therapy as first-line therapy for children prior to prescription of an antipsychotic.[4-6]

Due to known long-term adverse effects associated with long-term antipsychotic use and unknown benefits of use in young children, the following proposal was developed in conjunction with input from experts in child psychiatry and intends to support appropriate use of antipsychotics in children 5 years of age or less. The proposal targets children after their first prescription in order to accommodate prescribing for urgent or acute symptoms and to avoid interruptions in therapy during transitions of care for patients newly enrolled in Medicaid. Ongoing therapy will require documentation of clinical rationale, metabolic monitoring, use of first-line non-pharmacologic therapy, and specialist consult. Upon their first claim for an antipsychotic, outreach will be conducted for prescribers of the antipsychotic in order to assess appropriateness of care, provide education on evidence-based use of non-pharmacological therapy, and facilitate access to services for appropriate patients. A flowchart of the proposed process to perform provider outreach and facilitate access of antipsychotics for appropriate patients is available in **Appendix 2**.

Recommendation:

- Implement a safety edit to ensure appropriate use of antipsychotics in children 5 year of age or less (**Appendix 1**).
- Implement a retrospective provider outreach program to facilitate access to medications for appropriate children (**Appendix 2**).

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Antipsychotic Use in Children

Goal(s):

- Ensure safe and appropriate use of antipsychotics in children
- Discourage off-label use not supported by compendia

Length of Authorization:

- Up to 12 months

Requires PA:

- Antipsychotic use beyond 30 days in children 3-5 years of age
- All antipsychotic use in children 2 years of age or younger

Note: use of olanzapine as an antiemetic for chemotherapy does not require PA

Covered Alternatives:

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

Table 1. FDA-Approved Indications and Ages for Oral Second-generation Antipsychotics in Children

FDA-Approved Indications and Ages				
Drug	**Schizophrenia**	**Bipolar I disorder**	**Major depressive disorder (adjunct)**	**Other**
Second Generation Antipsychotics				
aripiprazole	≥13 yrs	≥10 yrs	≥18 yrs	Irritability associated with Autistic Disorder ≥6 yrs Tourette's Disorder ≥6 yrs
asenapine maleate	≥18 yrs	≥10 yrs		
lurasidone HCl	≥13 yrs	≥10 yrs		
olanzapine	≥13 yrs	≥13 yrs	≥18 yrs	
paliperidone	≥12 yrs			Schizoaffective disorder ≥18 yrs
quetiapine fumarate	≥13 yrs	≥10 yrs		Bipolar depression ≥18 yrs
risperidone	≥13 yrs	≥10 yrs		Irritability associated with Autistic Disorder ≥5 yrs

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for use of olanzapine as an antiemetic associated with cancer or chemotherapy?	**Yes:** Approve for 12 months	**No:** Go to #3
3. Has the patient been screened for diabetes (blood glucose or A1C) within the last 12 months?	**Yes:** Go to #5	**No:** Go to #4
4. Is there documented clinical rationale for lack of metabolic monitoring (e.g. combative behaviors requiring sedation)? Note: Caregivers failing to take patients to the laboratory is not a clinical rationale for lack of monitoring.	**Yes:** Document rationale. Go to #5	**No:** Pass to RPh. Deny; medical appropriateness. Annual metabolic screening is required for chronic use of antipsychotics. Refer denied requests to the OHA for follow-up. A single 90 day continuation of therapy may be granted upon request to allow for laboratory testing.

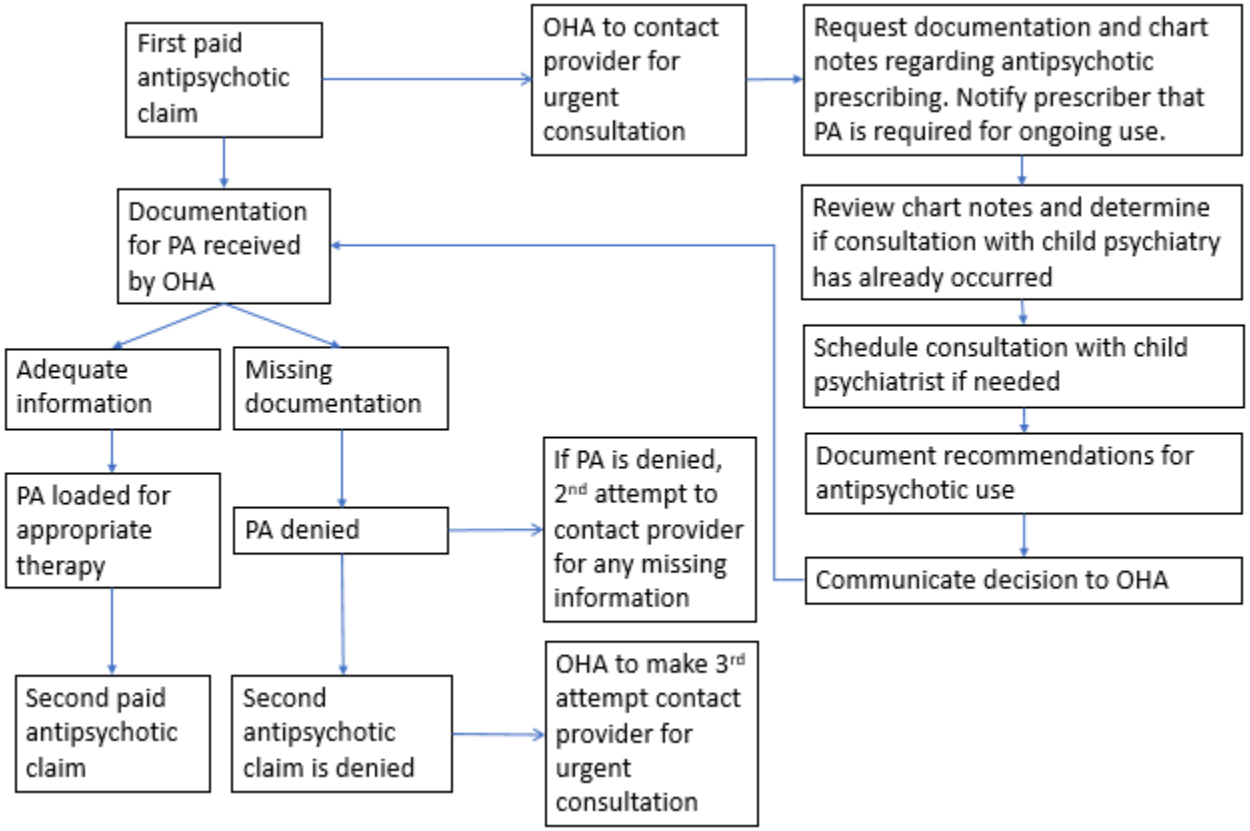
Approval Criteria		
5. Is the patient engaged in, been referred for, or have documented inability to access evidence based first-line non-pharmacological therapy (e.g., applied behavior analysis therapy for autism, parent behavioral therapy, or parent child interaction therapy)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness. Refer denied requests to the OHA for follow-up. A single 90 day continuation of therapy may be granted upon request to allow time for engagement.
6. Is the drug prescribed by or in consultation with a child psychiatrist or developmental pediatrician?	**Yes:** Approve for up to 12 months or length of therapy, whichever is less	**No:** Go to #7

Approval Criteria		
7. Is there detailed documentation regarding risk/benefit assessment and the decision to prescribe antipsychotic therapy? A thorough assessment should include ALL the following: a. Multidisciplinary review including a mental health specialist b. Mental health assessment including documentation of diagnoses, symptoms, and disease severity c. Discussion and consideration of first-line non-pharmacological therapies d. Assessment of antipsychotic risks and monitoring strategies e. Specific therapeutic goals of antipsychotic therapy, and for ongoing therapy, discussion of progress toward or achievement of therapeutic goals (or reasons for lack of progress and remediation strategies) f. Anticipated duration of therapy g. Detailed follow-up plan	**Yes:** Approve for up to 12 months or length of therapy, whichever is less	**No:** Pass to RPh. Deny; medical appropriateness. Refer denied requests to the OHA for follow-up. A single 90 day continuation of therapy may be granted upon request to allow for submission of required documentation.

P&T/DUR Review: 8/21(SS)
Implementation: TBD

Appendix 2. Provider notification Retrospective safety program to facilitate review of antipsychotic use in children less than 5 years of age

Figure A1. Notification process



Provider Notification

- Inclusion criteria will target 3 basic patient populations:
    1. Patients with a soon-to-expire PA based on the following criteria OR
        - Patients <= 5 years of age AND
        - a prior authorization for an antipsychotic with an expiration date within the next 30 days (PDL classes: antipsychotics, 1st gen; antipsychotics, 2nd gen; antipsychotics, parenteral) AND
        - a recent paid FFS claim for an antipsychotic in past 45 days AND
        - no subsequent prior authorization request approved for an antipsychotic
    2. Patients with a new start of an antipsychotic in the past 2 weeks defined based on the following criteria OR
        - Patients <= 5 years of age AND
        - with a paid FFS antipsychotic claim in the past 2 weeks AND
        - no currently active prior authorization for the antipsychotic AND
        - no paid claims for the same HSN within the prior 3 months.

3. Patients with a denied claim for an antipsychotic defined based on the following criteria
    - Patients <= 5 years of age AND
    - with a denied FFS antipsychotic claim in the past 2 weeks due to the safety edit AND
    - with no currently active prior authorization for the antipsychotic AND
    - with no subsequent paid claims for the same HSN

- Exclusion criteria:
    1. Providers with notifications sent for the same patient and drug (based on HSN) in the past 3 months
    2. Patients with a currently authorized PA for the same GSN as the identified paid antipsychotic claim
    3. Patients not currently enrolled in Medicaid
    4. Patients who are deceased

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

Oregon Health Authority
Kate Brown, Governor

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

Date issued: <Month Day, Year>

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

For billing ID: «Billing_Provider_Medicaid_ID»

Patient Safety Notice for Antipsychotic Use in Young Children for:
Patient: Billy Smith; DOB: 10/10/2017; Medicaid#: 12345; Drug: risperidone 0.5 mg tablet

Effective XX/XX/2021, the Oregon Health Authority (OHA) has implemented safety edits for children under 6 years old prescribed off-label antipsychotics. These edits are intended to encourage appropriate evidence-based care and are focused on optimal outcomes for children prescribed antipsychotics. Your collaboration with this initiative is highly valued.

This notice was generated to support appropriate care because:

- your NPI was linked to a paid antipsychotic claim for this patient AND
- documentation of medical necessity and appropriateness will be required for ongoing use

What should you do?

- Consider consultation with a child psychiatrist and referral for evidence-based non-pharmacologic therapy.
  - For young children with autism, consider applied behavior analysis (ABA) therapy or other well-supported models shown to reduce self-injury and other symptoms of autism.
  - For other behavioral health diagnoses, consider Parent Child Interaction Therapy (PCIT).
- For any patient where benefits of antipsychotic use outweigh risks, please request a prior authorization (PA). PA requests should document all the following:
  - Laboratory monitoring for diabetes
  - Discussion of first-line, evidence-based non-pharmacological therapy
  - Consultation with a child psychiatrist or developmental pediatrician OR an assessment of risks, benefits, and decision to prescribe antipsychotics. A thorough risk/benefit assessment should include all the following:
    - a multidisciplinary review
    - a mental health evaluation (including diagnoses, symptoms and disease severity)
    - specific therapeutic goals and anticipated length of therapy
    - monitoring strategies for adverse events (e.g., tardive dyskinesia, weight gain, etc.)
    - a detailed follow-up plan
- You can submit PA requests three ways:
  - Call the Oregon Pharmacy Call Center at 888-202-2126;
  - Submit via the secure Provider Web Portal at https://www.or-medicaid.gov; or
  - Fax to 888-346-0178. Use the form at https://apps.state.or.us/Forms/Served/oe3978.pdf.

Questions?

- For questions about this message, email OHA's Pharmacy Program at DMAP.RXQUESTIONS@dhsoha.state.or.us
- For additional information and resources on alternative psychiatric options for children visit the following websites:
  - Provider consultation and support: https://www.oregon.gov/oha/HSD/BH-Child-Family/Pages/Supports.aspx
  - Evidence-based treatments: https://www.oregon.gov/oha/HSD/BH-Child-Family/Pages/Early-Childhood.aspx

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

Prior Authorization Criteria Update: Growth Hormones

Purpose of Update:

The purpose of this prior authorization (PA) update is to align fee-for-service PA criteria with the current Health Evidence Review Commission (HERC) guidance for use of growth hormones (GH) and their FDA-approved indications. Growth hormones are indicated for a variety of childhood and adult conditions. HERC guidance restricts use of GH to funded diagnoses where there is medical evidence of effectiveness and safety. FDA-approved indications for GH vary by brand name product and are presented in **Table 1**. HERC guidance continues to specify that treatment with GH for children with conditions such as gonadal dysfunction, panhypopituitarism, iatrogenic and other pituitary disorders should only continue until adult height, as determined by bone age, is achieved.[1] Treatment for adult human growth hormone deficiency is currently not listed as a funded condition on the prioritized list.[1] However, funded conditions such as HIV associated with cachexia and short bowel syndrome are covered for adults by FDA-approved GH agents.

Table 1. Pediatric and Adults FDA Approved Indications for Growth Hormone[2,3]

	somatropin									somapacitan
	Genotropin®	**Humatrope®**	**Norditropin®**	**Nutropin AQ®**	**Omnitrope®**	**Saizen®**	**Serostim®**	**Zorbtive®**	**Zomacton®**	**Sogroya®**
Pediatric Indications										
GHD	X	X	X	X	X	X			X	
Prader-Willi Syndrome	X		X		X					
Noonan Syndrome			X							
Turner Syndrome	X	X	X	X	X				X	
Idiopathic Short Stature	X	X	X	X	X				X	
SHOX Deficiency		X							X	
CKD with Growth Failure				X						
Small for Gestational Age	X	X	X		X				X	

HIV Associated Cachexia							X			
Adult Indications										
GHD	X	X	X	X	X	X			X	X
HIV Associated Cachexia							X			
Short Bowel Syndrome								X		

Abbreviations: CKD = chronic kidney disease; FDA = Food and Drug Administration; GHD = growth hormone deficiency; HIV = human immunodeficiency virus; SHOX = Short stature homeobox-containing gene

Recommendation:

- Add somapacitan-beco to Growth Hormone PDL class and make non-preferred.
- Update the prior authorization criteria to align with HERC coverage guidance and FDA-approved indications.

References:

1. Health Evidence Review Commission. HERC Prioritized List of Health Services. February 1, 2021. https://www.oregon.gov/oha/HPA/DSI-HERC/PrioritizedList/2-1-2021%20Prioritized%20List%20of%20Health%20Services.pdf. Accessed March 10, 2021.
2. Somatropin, E-Coli Derived. In: IBM Micromedex® DRUGDEX® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. https://www-micromedexsolutions-com.liboff.ohsu.edu/ Accessed March 10, 2021.
3. Somatropin. In: Lexicomp (electronic database). Wolters Kluwer. Hudson, OH. http://online.lexi.com.liboff.ohsu.edu/action/home. Accessed March 10, 2021.

Growth Hormones

Goal(s):
- Restrict use of growth hormone (GH) for funded diagnoses where there is medical evidence of effectiveness and safety.

NOTE: Treatment with GH in children should continue only until adult height as determined by bone age is achieved. Treatment is not included for isolated deficiency of human growth hormone in adults.

Length of Authorization:
- Up to 12 months

Requires PA:
- All GH products require prior authorization for OHP coverage. Treatment of human growth hormone deficiency for adults is not funded by the OHP.

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

Initial Approval Criteria		
1. What is the diagnosis being treated?	Record ICD10 code	
2. Is the request for an FDA approved indication?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is this a request for initiation of growth hormone?	**Yes:** Go to #4	**No:** Go to **Renewal Criteria**
4. Is the patient an adult (>18 years of age)?	**Yes:** Go to #10	**No:** Go to #5
5. Is the agent being prescribed by, or in consultation with, a pediatric endocrinologist or pediatric nephrologist?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness

Initial Approval Criteria		
6. Is the diagnosis funded?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the diagnosis promotion of growth delay in a child with 3rd degree burns?	**Yes:** Document and send to DHS Medical Director for review and pending approval	**No:** Go to #8
8. If male, is bone age <16 years? If female, is bone age <14 years?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Is there evidence of non-closure of epiphyseal plate?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness
10. Is the request for the treatment of isolated human growth hormone deficiency in an adult (E23.0) or short stature due to an endocrine disorder (E34.3), or another unfunded condition? Per Guideline Note 74, treatment with GH for children with conditions such as panhypopituitarism, iatrogenic and other pituitary disorders, as well as gonadal dysfunction, should only continue until adult height, as determined by bone age, is achieved.	**Yes:** Pass to RPh. Deny; not funded by the OHP.	**No:** Go to #11
11. Is the requested product preferred?	**Yes:** Approve for up to 12 months	**No:** Go to #12
12. Will the prescriber consider a change to a preferred product that is FDA-approved for the condition? <u>Message</u>: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class and approve for up to 12 months.	**No:** Approve for up to 12 months

Renewal Criteria		
1. Document approximate date of initiation of therapy and diagnosis (if not already done).		
2. Was treatment with this agent initiated in patient prior to reaching adulthood (<18 years of age)?	**Yes:** Go to #3	**No:** Go to #5
3. Is growth velocity greater than 2.5 cm per year?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is male bone age <16 years or female bone age <14 years?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the request for isolated human growth hormone deficiency in an adult (E23.0), short stature due to an endocrine disorder (E34.3), or another unfunded condition?	**Yes:** Pass to RPh. Deny; not funded by the OHP.	**No:** Go to #6
6. Is the product requested preferred?	**Yes:** Approve for up to 12 months	**No:** Go to #7
7. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class and approve for up to 12 months	**No:** Approve for up to 12 months

P&T Review: 6/21 (DE); 11/18 ; 9/17; 9/16; 9/15; 9/14; 9/10; 5/10; 9/08; 2/06; 11/03; 9/03
Implementation: 1/1/19; 10/13/16; 1/1/11, 7/1/10, 4/15/09, 10/1/03, 9/1/06; 10/1/03

Trade Name (generic)

Sogroya (somapacitan-beco)

Indications

- Human growth hormone for the replacement of endogenous growth hormone (GH) in adults with growth hormone deficiency (GHD).
- This indication is an unfunded condition based on Oregon Health Plan (OHP) prioritized list (line 653; guideline note 74)

Dosage

- Initiation: 1.5 mg subcutaneously (SUBQ) once weekly for treatment naïve patients and patients switching from daily GH; 1 mg once weekly in patients aged 65 and older; 2 mg once weekly in women receiving oral estrogen
- Increase weekly dosage by 0.5 mg to 1.5 mg increments every 2 to 4 weeks until desired response has been achieved; Maximum dose is 8 mg once weekly
- Supplied as a 10 mg/1.5 ml (6.7 mg/ml) single-patient-use prefilled pen; pen delivers doses from 0.05 mg to 4.0 mg, in increments of 0.05 mg.

Background

- Binds to a dimeric growth hormone receptor in the cell membrane of target cells resulting in intracellular signal transduction.
- Pharmacodynamic effects aim to mimic action of endogenous GH leading to increase in insulin-like growth factor 1 (IGF-1) levels and improvement in body composition.

Efficacy

FDA-approval was based on a 35-week, phase 3, double-blind, placebo-controlled study [NCT02229851]. The trial enrolled 300 treatment naïve adult growth hormone-deficient patients (AGHD) randomized (2:1:2) to receive somapacitan SUBQ once-weekly injection (n=120), once-weekly placebo (n=61), or an open-label daily dose of somatropin SUBQ injection (n=119). Trial completers were enrolled in a 52-week open-label extension period where placebo group patients were switched to somapacitan while the daily somatropin group was randomized 1:1 to continue once daily somatropin or once weekly somapacitan. Participants were mostly white (67%) or Asian (29%) with a mean age of 45 years and evenly divided by sex. The mean baseline body mass index (BMI) was 27.4 kg/m^2. The primary efficacy outcome was change from baseline to week 34 in truncal fat percentage* as assessed by dual X-ray absorptiometry. The manufacturer did not prespecify thresholds for changes in body composition as evidence GH effectiveness. Although statistical significance was reached for the primary endpoint, the FDA noted that none of the observed improvements in body composition in patients with GHD have been directly linked to an outcome of morbidity/mortality reduction and none of the trials established that use of GH in patients with AGHD reduce cardiovascular risk or mortality.

FDA Results for Primary Outcome Measures	Weekly Placebo	Weekly Somapacitan	Daily Somatropin
Number of subjects in full analysis (N)	61	120	119
Truncal fat % change at 34 weeks from baseline	+0.31	-1.10	-2.38
Absolute Treatment Difference vs Placebo (%) 95% [Confidence Interval]; p-value	-1.41 [-2.61 to -0.22]; 0.02		
Absolute Treatment Difference vs Daily Somatropin (%) 95% [Confidence Interval]; p-value		+1.28% (95% CI: 0.29%, 2.26%); 0.011	

*Truncal fat % = (truncal fat mass)/(truncal fat mass + truncal lean body mass) x 100

Safety

Common adverse reactions: back pain (10%), arthralgia (7%), dyspepsia (5%), sleep disorder (4%), dizziness (4%), tonsillitis (3%), peripheral edema (3%), vomiting (3%), adrenal insufficiency (3%), hypertension (3%), blood creatine phosphokinase increase (3%), weight increased (3%), anemia (3%)
Contraindications: acute critical illness after open-heart or abdominal surgery, multiple accidental trauma, or those with acute respiratory failure; active malignancy; active proliferative or severe non-proliferative diabetic retinopathy
Warnings and Precautions: Increased mortality in patients with acute critical illness, increased risk of neoplasms, glucose intolerance and diabetes mellitus, intracranial hypertension, severe hypersensitivity including anaphylaxis and angioedema, fluid retention, hypoadrenalism, hypothyroidism, pancreatitis, lipohypertrophy/lipoatrophy
Special Populations: Reduce initial dose in elderly (≥65 years) and those with moderate hepatic impairment; avoid use in severe hepatic impairment

Evidence Gaps/Limitations

- There is no evidence that GH treatments affect mortality or major morbidity.
- Although no statistical non-inferiority was pre-specified or required, somapacitan found to be inferior to daily somatropin with the magnitude of difference almost as much as the difference between somapacitan and placebo.

Recommendation

Restrict use for OHP-covered conditions through Prior Authorization

References

1. Sogroya (somapacitan-beco) for subcutaneous injection [Prescribing Information]. Plainsboro, NJ, USA. Novo Nordisk Inc, 2020.
2. FDA Center for Drug Evaluation and Research. Sogroya Sum. Review. Application Number 761156Orig1s000. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/761156Orig1s000SumR.pdf

Drug Use Research & Management Program
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Drug Class Update with New Drug Evaluation: Hereditary Angioedema

Date of Review: June 2021

Date of Last Review: March 2019
Dates of Literature Search: 01/01/2019 - 01/07/2021
Generic Name: berotralstat
Brand Name (Manufacturer): Orladeyo™ (BioCryst Pharmaceuticals, Inc)
Dossier Received: yes

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

Purpose for Class Update:
The purpose of this class update is to evaluate place in therapy for a new oral therapy for prophylaxis of hereditary angioedema (HAE) attacks.

Research Questions:
1. What is the comparative evidence for efficacy and harms of prophylactic therapy for HAE?
2. What is the efficacy and safety of berotralstat for prophylactic treatment of HAE attacks?
3. Are there subpopulations of patients with HAE for which treatment may be more effective or associated with more harms?

Conclusions:
- There is no new direct comparative evidence evaluating drugs for prophylaxis or acute treatment of HAE. Since the last review of this class, subcutaneous C1 esterase inhibitor concentrate from human plasma (Haegarda®) received an expanded indication for routine prophylaxis of hereditary angioedema attacks in patients 6-12 years of age.[1]
- Efficacy and safety of berotralstat was primarily based on a single, small, phase 3 trial evaluating efficacy over 24 weeks (n=121).[2]
- There is insufficient evidence evaluating efficacy of berotralstat to current prophylactic therapy for HAE. In patients with an average baseline of 3 HAE attacks per month, ongoing prophylactic use of berotralstat 150 mg daily decreases, but does not eliminate, HAE attacks compared to placebo (1.35 vs. 2.35 attacks per month; RR 0.56; 95% CI 0.41 to 0.77; p<0.001; low quality evidence).[3] All patients enrolled in the trial were required to have access to acute treatment for HAE attacks.
- There was no difference in quality of life for patients treated with berotralstat compared to placebo (insufficient evidence).[3] Berotralstat has not been studied for the treatment of acute attacks or for short-term prophylactic therapy prior to surgery. There is no evidence that prophylactic use of berotralstat treatments affects mortality, hospitalization rate, or has long-term impacts on work, school, depression or anxiety.
- The most common adverse events (AE) associated with berotralstatwere gastrointestinal and primarily resolved with time.[2] Safety labeling includes warnings for QT prolongation and elevated liver enzymes.[2] There is insufficient data to evaluate long-term safety outcomes.

Author: Sarah Servid, PharmD

Recommendations:

- Update prior authorization criteria to include berotralstat.
- No changes to the PDL recommendations based on clinical evidence. Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy

- Therapy for HAE can be divided into 2 types: acute and prophylactic treatment. There is no direct comparative evidence evaluating drugs for either prophylactic or acute treatment of HAE.
- With acute use for treatment of a HAE attack, time to symptom relief or resolution was improved by approximately 1-2 hours compared to placebo with human or recombinant C1 inhibitors or kallikrein inhibitors (low quality evidence).[4-8] The clinical benefit of a 1-2 hour improvement in symptoms in unclear, and there is insufficient evidence to evaluate efficacy of drugs in patients with laryngeal attacks.
- In patients with a frequent history of angioedema attacks (baseline rate of 3-4 per month), prophylactic use of C1 esterase inhibitors was associated with a mean reduction of 2.1 to 3.5 attacks per month over 12 to 16 weeks compared to placebo (low to moderate quality evidence).[9] With prophylactic use of lanadelumab compared to placebo in patients with a baseline rate of 3-4 attacks per month, the average angioedema attack rate was reduced by 1.5 to 1.7 attacks per month compared to placebo (moderate quality evidence).[9]
- There is insufficient evidence that prophylactic use of HAE treatments affects mortality, hospitalization rate, quality of life, or long-term impacts on work, school, depression or anxiety.

Background:

Hereditary angioedema (HAE) is caused by a deficiency or lack of function of C1 inhibitor protein.[10,11] C1 inhibitor is an important regulator of the complement system and the kallikrein-kinin pathway which is involved in formation of bradykinin.[11] A lack of functional C1 inhibitor protein can result in an overproduction of bradykinin which is the primary cause of swelling in patients with hereditary angioedema. The deficiency is most commonly hereditary, though it may also be acquired via increased catabolism of C1 inhibitor protein, often as a result of malignancy or autoantibodies, thereby decreasing inhibitor function. [11] Diagnosis is based on laboratory analysis of complement C4 and C2 levels and C1 inhibitor antigenic levels. [10,11] There are 3 types of HAE. Type 1 and type 2 are clinically indistinguishable from each other and account for the majority of cases of C1 inhibitor deficiency. Approximately 75% of patients diagnosed with HAE have a family history of angioedema. [11]

Symptoms of the disease include angioedema without urticaria which typically begin to present in early childhood or adolescence. Attacks of angioedema worsen gradually and resolve slowly over 24-72 hours. [11] Attacks may also be preceded by a prodromal phase with symptoms such as fatigue, non-urticarial rash, or other flu-like symptoms. Attacks most commonly involve the extremities and abdomen, but can be life-threatening if they involve the oropharynx or larynx. [11] Severity and frequency of attacks is highly variable between patients.[11] Frequency of attacks may be affected by hormone levels and often occur with onset of puberty, menopause, use of contraceptives, pregnancy, or other changes in estrogen levels. Hereditary angioedema is equally prevalent for males and females, though females may present with more frequent or severe symptoms due to changes in hormone levels. Precipitating factors for attacks are often unclear, though both stress and physical trauma have been correlated with onset of acute attacks. [10,11]

Current standard of care for treatment of acute attacks of angioedema include C1 inhibitors, ecallantide, or icatibant. Drugs that are FDA approved for acute and prophylactic therapy are shown in **Table 1**. While no high quality guidelines met inclusion criteria for this review, guidelines from the World Allergy Organization recommend on-demand therapy be considered for treatment of acute attacks of angioedema, and that any attack affecting the upper airway be treated (based

on expert consensus opinion).[10] Guidelines are limited by significant conflicts of interest and lack of details on guideline development methodology, with many recommendations based on expert consensus opinion. In general, early administration of medications is associated with better treatment response. [10] Recommended first-line prophylactic therapy includes a C1 inhibitor, though guidelines were published prior to FDA approval of lanadelumab-flyo or berotralstat.[10] No recommendations are made for a specific type of C1 inhibitor therapy. Administration of other anaphylactic therapy, such as epinephrine, antihistamines, and corticosteroids are only recommended if the cause of swelling and diagnosis of hereditary angioedema is unclear as these therapies do not improve symptoms of HAE attacks. [10]

Table 1. FDA-approved Indications and Dosing

Generic Name; Designation (Brand Name)	Indication(s)	Strength/Route	Dose and Frequency
Acute Treatment			
C1 esterase inhibitor; C1-INH-B (Berinert®)	Treatment of acute abdominal, facial, or laryngeal HAE attacks in adults and pediatric patients	500 units IV kit	20 units/kg as a single dose
C1 esterase inhibitor, recombinant ; C1-INH-R (Ruconest®)	Treatment of acute HAE attacks in adult and adolescent patients. Efficacy has not been established in laryngeal attacks	2100 units IV reconstituted solution	50 units/kg as a single dose; maximum dose: 4,200 units
Ecallantide (Kalbitor®)	Treatment of acute HAE attacks in patients 12 years and older	10 mg/mL SC solution	30 mg as a one-time dose (3 injections); may repeat once within 24 hours if attack continues
Icatibant (Firazyr®)	Treatment of acute HAE attacks in patients 18 years and older	10 mg/mL SC solution	30 mg once; may repeat every 6 hours if response is inadequate; maximum dose per day: 90 mg
Prophylactic Treatment			
Berotralstat (Orladeyo™)	HAE prophylaxis in patients ≥12 years of age	110 or 150 mg orally	150 mg daily; 110 mg daily recommended for patients with moderate to severe hepatic impairment or significant drug interactions
C1 esterase inhibitor ; C1-INH-C (Cinryze®)	HAE prophylaxis in adults, adolescents, and pediatric patients ≥6 years of age	500 units IV reconstituted solution	1,000 units every 3 to 4 days (twice weekly); doses up to 2,500 units (≤100 units/kg) every 3 or 4 days may be considered based on individual patient response.
C1 esterase inhibitor; C1-INH-H (Haegarda®)	HAE prophylaxis in adults and adolescents	2000 and 3000 units SC reconstituted solution	60 units/kg every 3 to 4 days (twice weekly)
Lanadelumab-flyo (Takhzyro™)	HAE prophylaxis in patients ≥12 years of age	300 mg/2mL SC solution	300 mg every 2 weeks; may consider dosing every 4 weeks for patients who are well-controlled for > 6 months

Abbreviations: HAE = hereditary angioedema, IV = intravenous; SC = subcutaneous

While plasma-derived products are screened extensively, there is still a risk for transmission of infectious disease (i.e., viruses) with plasma-derived C1 inhibitors (C1-INH-B, C1-INH-C, C1-INH-H).[12-14] Other major safety concerns include hypersensitivity reactions and thrombotic events which have been reported with both plasma-derived and recombinant C1 inhibitors.[12-15] Anaphylaxis is also a concern with ecallantide (reported in 3-4% of patients in clinical trials) and with C1

esterase inhibitors (incidence unknown).[8,10,16] Hypersensitivity reactions were also documented in 1% of patients treated with lanadelumab-flyo compared to placebo.[17] It is recommended that epinephrine be immediately available with administration of all human-derived C1 esterase inhibitors due to the risk of anaphylaxis. After self-administration of treatment for laryngeal HAE attacks, patients should be instructed to seek immediate medical care due to the ongoing potential for airway obstruction during acute laryngeal attacks.[10,16-18]

Clinically relevant outcomes include improvements in mortality, hospitalization rate, attacks requiring intubation or treatment, symptom severity, and impacts on work, school, or quality of life. Common outcomes evaluated in clinical trials include time to symptom resolution during an acute attack and reduction in number of attacks over time with prophylactic treatment. There is no established or validated measure to evaluate symptom improvement in patients with HAE attacks, and clinical trials have used a variety of scales to evaluate symptom severity and quality of life.

In the fee-for-service (FFS) population, approximately 11 patients had a diagnosis indicating defects in the complement system (D84.1) over a recent one year period. This number may be an overestimate of patients as this diagnosis includes conditions with other types of complement deficiencies.

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 high quality systematic reviews were identified since the last review.

New Guidelines:
No new high quality guidelines were identified since the last review.

New Formulations or Indications:
In September 2020, subcutaneous C1 esterase inhibitor concentrate from human plasma (Haegarda®) received an expanded indication for routine prophylaxis of hereditary angioedema attacks in patients 6 years and older.[1] The product was previously approved in adults and adolescents and expanded approval in children was based on a phase 3, open-label, long-term safety study. Nine pediatric patients ages 8 to 16 were included. Upon analysis by age, results were similar to the overall population.[1]

New FDA Safety Alerts:
No new safety alerts identified.

Randomized Controlled Trials:
A total of 21 citations were manually reviewed from the initial literature search. After further review, 19 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 trials are summarized in the evidence table for berotralstat below.

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:
Berotralstat was FDA approved based on a single phase 3, double-blind, placebo-controlled clinical trial of 121 patients with type 1 or 2 HAE.[3] Included patients were primarily White (>95%), and had an average of 3 HAE attacks per month. Most patients (approximately 75%) had a history of other prophylactic treatment for HAE.[3] Patients with fewer than 2 attacks over 8 weeks were excluded.[3] The primary endpoint was improvement in investigator-confirmed HAE attacks per month over 24 weeks. Secondary endpoints included change in quality of life, measured by the AE-QOL questionnaire, and number of days with angioedema symptoms. A second, similarly designed, smaller phase 3 trial including 19 patients was conducted in Japan.[19]

Trial limitations included slight variability between groups in prior treatments, age, gender, and body mass index (BMI) likely due to small sample sizes.[3] Groups were blinded with use of matched placebo, though characteristics of the placebo were not described, and differential rates of dose-related gastrointestinal AE between groups increases risk for potential unblinding. The majority of study authors had conflicts of interest including pending patents, personal fees from the manufacturer, or positions on speaker or advisory boards.[3] Applicability was limited to patients with frequent attacks (at least 2 per month). While patients were required to have at least 2 attacks during the screening period which impacted function or required treatment, the primary outcome evaluated all HAE attacks, not only those requiring treatment.[3] Confirmation of swelling was required to diagnose an attack, but it was unclear whether criteria was standardized between investigators for identification of attacks from patient diaries.

At 24 weeks compared to placebo, the number of investigator confirmed attacks per month was improved with both 110 mg (1.65 vs. 2.35; RR 0.70; 95% CI 0.51 to 0.95; p=0.024) and 150 mg (1.35 vs. 2.35; RR 0.56; 95% CI 0.41 to 0.77; p<0.001).[3] Similar trends were observed in the study in Japan, though results failed to achieve statistical significance for the 110 mg dose.[19] Authors noted that the study conducted in Japan had a small number of patients enrolled and was underpowered which is reflected in wide confidence intervals for the primary endpoint.[19] In the primary trial, there was no statistical difference observed for the secondary endpoint evaluating quality of life.[3] Other secondary endpoints were considered to be non-significant based on the pre-specified hierarchical testing plan.[3]

There is insufficient evidence evaluating efficacy of berotralstat to current prophylactic therapy for HAE. Trials to evaluate long-term efficacy and safety are ongoing. In patients with 2 or more HAE attacks per month, ongoing prophylactic use of berotralstat decreases, but does not eliminate HAE attacks. There is insufficient evidence that berotralstat does not improve quality of life for patients with HAE compared to placebo. There is currently no evidence for use in treatment of acute attacks or for short-term prophylactic therapy prior to surgery.

Clinical Safety:
Safety data for berotralstat was primarily based on a single, small, phase 3 trial evaluating efficacy over 24 weeks (n=121).[2] Few serious adverse events occurred during the trial, and the number of patients discontinuing treatment due to an adverse event was small (4 patients treated with berotralstat compared to 1 treated with placebo).[3]

Common adverse events occurring with berotralstat included abdominal pain, vomiting, diarrhea, back pain and gastroesophageal reflux disease (**Table 1**).[2] Gastrointestinal adverse events were dose dependent. Most gastrointestinal adverse events did not require intervention and typically self-resolved with time. However, use of the lower 110 mg dose is recommended in patients unable to tolerate 150 mg daily.[2]

Table 1. Common adverse events associated with berotralstat[2]

	Berotralstat* N (%)	**Placebo N (%)**	**Percent Difference**
Diarrhea	10 (12%)	0 (0%)	12%
Vomiting	10 (12%)	1 (3%)	9%
Gastroesophageal reflux disease	6 (7%)	0 (0%)	7%
Abdominal pain	13 (16%)	4 (10%)	6%
Back pain	5 (6%)	1 (3%)	3%

* Incidence for 110 and 150 mg daily combined

Labeling for berotralstat includes risks for QT prolongation with doses over 150 mg daily.[2] Liver-related adverse events also occurred in 3 patients treated with berotralstat including asymptomatic elevated transaminases (ALT >8x and AST >3x the upper limit of normal).[2] Berotralstat is metabolized by CYP enzymes and dose adjustment is recommended for patients with moderate or severe liver impairment to mitigate risk for QT prolongation.[2] Dose adjustment is also recommended in patients prescribed p-glycoprotein or BCRP inhibitors (e.g., cyclosporine).[2] Concomitant use of berotralstat with p-gp inducers is not recommended due to potential for decreased efficacy.[2]

There are insufficient data to assess the long-term safety of berotralstat. While berotralstat is FDA-approved in adolescents at least 12 years of age, only 16 adolescent patients were enrolled in clinical trials.[2] Similarly, a small number of geriatric patients 65 years or older were enrolled in clinical trials (n=14).[2] Subgroup analyses based on age identified no additional safety concerns in these populations, but data are significantly limited by the small number of patients included in clinical trials which limits ability to detect rare, but serious, adverse events.

Look-alike / Sound-alike Error Risk Potential: Berotralstat may be confused with belinostat or vorinostat, drugs used for the treatment of T-cell lymphoma.

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Hospitalizations
2) HAE attacks requiring treatment or intubation
3) HAE symptom severity (e.g., swelling, etc)
4) Functional improvement (e.g., missed work/school, etc)
5) Serious adverse events
6) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Investigator-confirmed HAE attacks per month

Table 2. Pharmacology and Pharmacokinetic Properties.[2]

Parameter	
Mechanism of Action	Berotralstat is a kallikrein inhibitor. Inhibition of kallikrein results in reduced blood levels of bradykinin thereby decreasing vascular permeability and edema in patients with HAE. Patients with C1-inhibitor deficiency (a endogenous kallikrein inhibitor) have increased activity of kallikrein which results in HAE symptoms.
Oral Bioavailability	Not reported
Distribution and Protein Binding	Protein binding: 99%
Elimination	9% excreted in urine and 79% excreted in feces
Half-Life	Median 93 hours (range: 39 to 152 hours)
Metabolism	Substrate of BCRP and p-glycoprotein. Metabolized by CYP2D6 and CYP3A4 enzymes.

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. Zuraw, et al.[3] Phase 3, DB, PC, PG, MC, RCT	1. berotralstat 110 mg once daily 2. berotralstat 150 mg once daily 3. Placebo Run-in period of up to 70 days was used to evaluate baseline attack rate Acute treatment of attacks followed the patient's usual medical management Duration: 24 weeks	Demographics: - Age (SD) 1. 40 (17.5) 2. 40 (14.0) 3. 45 (14.1) - Female: 58-73% - White: 93-95% - North America: 68-78% - Normal BMI: 20-46% - Mean HAE attacks (SD) 1. 2.97 (1.36) 2. 3.06 (1.56) 3. 2.91 (1.12) - HAE attacks ≥2/month 1. 68% 2. 75% 3. 68% - Prior HAE tx: 73-78% - Prior C1-INH tx: 39-53% - Prior androgen tx: 46-63% Key Inclusion Criteria: - Age ≥12 years in Canada/US or ≥ 18 years in Europe - HAE type 1 or 2 confirmed by one of the following: - C1-INH functional level <50% and C4 level < LLN - C1-INH functional level 50%-74% with single-repeat level <50% or a pathogenic SERPING1 mutation - C4 level > LLN with low C4 during a HAE attack, physician confirmed family history of C1-INH deficiency or pathogenic SERPING1 - ≥ 2 attacks in 8 weeks with functional impairment or requiring treatment	ITT: 1. 41 2. 40 3. 40 Attrition: 1. 4 (9.8%) 2. 3 (7.5%) 3. 5 (12.5%)	Primary Endpoint: Investigator-confirmed HAE attacks per month 1. 1.65 2. 1.35 3. 2.35 1 vs. 3: RR 0.70 (95% CI 0.51-0.95); p=0.024 2 vs. 3: RR 0.56 (95% CI 0.41-0.77); p<0.001 Secondary Endpoints: Mean change in AE-QoL from baseline to week 24 (range 0-100) 1. –12.46 (SE 2.53) 2. –14.59 (SE 2.59) 3. –9.69 (SE 2.64) 1 vs. 3: –2.77 (–10.08 to 4.53); p = 0.453 2 vs. 3: –4.90 (–12.23 to 2.43); p = 0.118 Proportion of days with angioedema symptoms 1. 0.134 (SE 0.019) 2. 0.119 (SE 0.019) 3. 0.197 (SE 0.020) 1 vs. 3: –0.062 (95% CI –0.117 to –0.008)* 2 vs. 3: –0.078 (95% CI –0.133 to –0.023)* Mean number of days with angioedema symptoms 1. 20.8 (SD 19.22) 2. 19.4 (SD 21.50) 3. 29.2 (SD 24.29) Difference NR* *NS based on pre-specified hierarchical testing plan	 NA NA NS NS NS NS NS	DC due to AE 1. 3 (7.3%) 2. 1 (2.5%) 3. 1 (2.5%) Treatment emergent SAE 1. 1 (2.4%) 2. 0 (0%) 3. 3 (7.5%) Treatment emergent AE 1. 34 (83%) 2. 34 (85%) 3. 30 (77%) Gastro-intestinal abdominal treatment emergent AE 1. 17 (42%) 2. 20 (50%) 3. 14 (36%)	N/A For all	**Risk of Bias (low/high/unclear)**: Fair Selection Bias: Low. Randomized using interactive web response system. Stratified by baseline attack rate (< or ≥ 2 per month). Patients, investigators, site and sponsor personnel blinded to allocation. Slight variability between groups in prior treatments, age, gender, and BMI likely due to small sample sizes. Performance Bias: Unclear. Patients, investigators, site and sponsor personnel blinded via matching placebo. Differential rates of dose-related gastrointestinal AE between groups increases risk for potential unblinding. Detection Bias: Unclear. Patients and investigators blinded, but method of blinding unspecified. Use of patient reported diaries to document HAE attack symptoms with investigator follow-up and confirmation within 2 days. Confirmed swelling was a requirement to diagnose an attack, but it was unclear whether criteria was standardized between investigators for identification of attacks from patient diaries. Attrition Bias: Low. Attrition comparable between groups. ITT analysis used for efficacy outcomes. Reporting Bias: Low. Primary and secondary outcomes reported as pre-specified. Multiple post-hoc analyses. Other Bias: High. Study funded by manufacturer. Majority of authors with conflicts of interest including pending patents, personal fees from the manufacturer, or positions on speaker or advisory boards. Involvement of authors in data analysis was not reported. **Applicability**: Patient: Majority of patients were White. Patients included had frequent attacks (at least 2 attacks over 8 weeks); most patients had prior prophylactic therapy (75%) and a history of laryngeal attacks (74%). During the screening period, attacks had to cause functional impairment or require treatment. One-hundred sixty patients were screened and 121 had ≥2 attacks and enrolled. Intervention: Mean rate of compliance was 97-99% for all groups. Standard of care given for acute attacks. FDA-approved doses of 110 mg and 150 mg were evaluated. This trial demonstrated a small dose response. Doses were based on a phase 2 trial evaluating 62.5mg to 350mg. No statistical benefit was observed for 62.5mg dose compared to placebo, and doses of 250mg and 350 mg were not demonstrably different from the 125mg dose.[20]

		- Weight ≥ 40 kg Key Exclusion Criteria: - Use of androgen or tranexamic acid prophylaxis within 28 days or C1-INH prophylaxis within 14 days						Comparator: Placebo appropriate to determine efficacy. No comparison to available prophylactic therapies which would be useful to establish place in therapy. Outcomes: Primary endpoint counted all HAE attacks regardless of severity, not only those requiring treatment or functional impairment. Setting: 40 sites in 11 countries from March 14, 2018 to April 10, 2019. Numbers of patients in the US were not reported.
2. Ohsawa, et al.[19] Phase 3, DB, PC, PG, RCT	1. berotralstat 110 mg once daily 2. berotralstat 150 mg once daily 3. Placebo Run-in period of 56 days was used to determine eligibility and baseline HAE attacks Duration; 24 weeks Acute attacks were treated as needed by the investigator or treating physician	Demographics: - Mean age 42 years (SD 13) - Female: 84% - Asian: 94% - Mean BMI: 25 (SD 5) kg/m^2 - Attacks/month: 2.3 (SD 1.2) - HAE attacks ≥2/month: 48% - Prior prophylactic tx: 79% - C1-INH: 16% - Androgen: 16% - Tranexamic acid: 58% - Mean age at diagnosis: 31 (SD 14) - Missed work/education for HAE in prior year: 74% Key Inclusion Criteria: - Age ≥12 years - HAE type 1 or 2 (see Zuraw et al for specific diagnostic criteria) - ≥2 independent expert-confirmed HAE attacks during the run-in period Key Exclusion Criteria: - See Zuraw, et al	ITT: 1. 6 2. 7 3. 6 PP: 1. 6 2. 7 3. 5 Attrition: 1. 0 2. 0 3. 1 (17%)	Primary Endpoint: Expert-confirmed HAE attacks over 24 weeks 1. 1.64 2. 1.11 3. 2.18 1 vs. 3: RR 24.6% (95% CI −14.0 to 50.1); p=0.181 2 vs. 3: RR 49.1% (95% CI 20.4 to 67.5); p=0.003 Secondary Endpoints: Proportion of days with angioedema symptoms 1. 0.26 (SE 0.05) 2. 0.12 (SE 0.05) 3. 0.24 (SE 0.05) 1 vs. 3: 0.02 (95% CI −0.14 to 0.18); p=0.814* (mean of ~3 symptom free days) 2 vs. 3: −0.12 (95% CI −0.28 to 0.04); p=0.120 (~mean of ~20 symptom free days) Mean change in AE-QoL from baseline to week 24 (range 0-100) 1. −9.47 (SE 6.93) 2. −15.82 (SE 6.42) 3. 3.18 (SE 6.83) 1 vs. 3: −12.7 (95% CI −33.3 to 8.0); p=0.213 2 vs. 3: −19.0 (95% CI −39.0 to −1.0); NS* *NS based on pre-specified hierarchical testing plan	NS NA NS NS NS NS	Drug-related Treatment emergent AE 1. 2 (33%) 2. 2 (29%) 3. 2 (0%) DC due to AE 1. 0 (0%) 2. 0 (0%) 3. 1 (17%) Treatment emergent SAE 1. 1 (17%) 2. 0 (0%) 3. 0 (0%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized via interactive response system. Stratified by baseline attack rate (< or ≥ 2 attacks/month). Study drug assignment was blinded to the investigator, study staff, patients, and clinical research organization staff. Slight differences in baseline characteristics likely due to small sample sizes. Performance Bias: Unclear. Method of blinding not reported. Detection Bias: Unclear. Method of blinding unspecified. Use of patient reported diaries to document HAE attack symptoms with investigator follow-up and confirmation within 2 days. An independent expert reviewed information from all reported HAE attacks to confirm diagnosis. Attrition Bias: Low. Attrition comparable between groups. ITT analysis used for efficacy outcomes. Reporting Bias: Low. Outcomes reported as prespecified. Multiple post-hoc analyses reported. Other Bias: Unclear. Study funded by manufacturer. Majority of authors with conflicts of interest. Study was underpowered based on statistical power estimates and number of enrolled patients, which may result in limited ability to determine statistical differences between groups. **Applicability**: Patient: Of the 25 patients screened, 19 patients had ≥2 attacks and were randomized. Intervention: See Zuraw, et al. Comparator: See Zuraw, et al. Outcomes: Primary endpoint counted all HAE attacks regardless of severity, not only those requiring treatment or functional impairment. Attacks did not have to be unique events. Setting: 10 sites in Japan from December 2018 to November 2019.

Abbreviations [alphabetical order]: AE = adverse event; AE-QoL = Angioedema Quality of Life questionnaire; ARR = absolute risk reduction; BMI = body mass index; C1-INH = complement 1 inhibitor; C4 = complement 4; CI = confidence interval; DB = double blind; DC = discontinuation; HAE = hereditary angioedema; ITT = intention to treat; LLN = lower limit of normal; MC = multicenter; 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; NR = not reported; PC = placebo controlled; PG = parallel group; PP = per protocol; RCT = randomized controlled trial; SAE = severe adverse event; SD = standard deviation; SE = standard error

References:

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15. Ruconest (c1-esterase inhibitor, recombinant) [product information]. Bridgewater, NJ: Pharming Healthcare Inc. March 2018.
16. Firazyr (icatibant acetate) injection [product information]. Lexington, MA: Shire US Manufacturing, Inc. December 2015.
17. Takhzyro (lanadelumab-flyo) injection, for subcutaneous use [product information]. Lexington, MA: Dyax Corp. Nov 2018.

18. Kalbitor (ecallantide) injection, for subcutaneous use [product information]. Burlington, MA: Dyax Corp. Sept 2014.
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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
C1 esterase inhibitor	BERINERT	IV	KIT	Y
C1 esterase inhibitor	BERINERT	IV	VIAL	Y
C1 esterase inhibitor	HAEGARDA	SQ	VIAL	Y
berotralstat hydrochloride	ORLADEYO	PO	CAPSULE	
C1 esterase inhibitor	CINRYZE	IV	VIAL	N
C1 esterase inhibitor, recomb	RUCONEST	IV	VIAL	N
ecallantide	KALBITOR	SQ	VIAL	N
icatibant acetate	FIRAZYR	SQ	SYRINGE	N
icatibant acetate	ICATIBANT	SQ	SYRINGE	N
lanadelumab-flyo	TAKHZYRO	SQ	VIAL	N

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to January 07, 2021

1	exp Angioedemas, Hereditary/	1160
2	exp complement c1 inactivator proteins/ or exp complement c1 inhibitor protein/	2757
3	exp Bradykinin Receptor Antagonists/	1330
4	ecallantide.mp.	180
5	icatibant.mp.	1395
6	lanadelumab.mp.	44
7	berotralstat.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	3
8	BCX7353.mp.	5
9	2 or 3 or 4 or 5 or 6 or 7 or 8	4776
10	1 and 9	806
11	limit 10 to (english language and humans)	749
12	limit 11 to yr="2018 -Current"	157
13	limit 12 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or equivalence trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	21

Appendix 3: Prescribing Information Highlights

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

ORLADEYO™ (berotralstat) capsules, for oral use
Initial U.S. Approval: 2020

----------INDICATIONS AND USAGE----------
ORLADEYO is a plasma kallikrein inhibitor indicated for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adults and pediatric patients 12 years and older. (1)

Limitations of Use:
ORLADEYO should not be used for treatment of acute HAE attacks. (1)

----------DOSAGE AND ADMINISTRATION----------
- Recommended Dosage: One capsule (150 mg) taken orally once daily with food. (2.1)

See Full Prescribing Information for:
- Dosage adjustment in patients with moderate or severe hepatic impairment. (2.2)
- Dosage adjustment in patients with chronic administration of P-gp or BCRP inhibitors. (2.3)
- Dosage adjustment in patients with persistent gastrointestinal reactions. (2.4)

----------DOSAGE FORMS AND STRENGTH----------
Capsules: 150 mg, 110 mg (3)

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

----------WARNINGS AND PRECAUTIONS----------
An increase in QT prolongation can occur at dosages higher than the recommended 150 mg once daily dosage. Additional doses or doses of ORLADEYO higher than 150 mg once daily are not recommended. (5.1)

----------ADVERSE REACTIONS----------
Most common adverse reactions (≥10%) are abdominal pain, vomiting, diarrhea, back pain, and gastroesophageal reflux disease. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact BioCryst Pharmaceuticals, Inc. at 1-833-633-2279 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
P-gp or BCRP inhibitors – Reduce ORLADEYO dosage when co-administered. (7.1, 12.3)

P-gp inducers – Avoid use with ORLADEYO. (7.1)

CYP2D6, CYP3A4 or P-gp Substrates: Appropriately monitor or dose titrate narrow therapeutic index drugs that are predominantly metabolized by CYP2D6, CYP3A4 or are P-gp substrates when co-administered with ORLADEYO. (7.2, 12.3)

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

Revised: 12/2020

Appendix 4: Key Inclusion Criteria

Population	Patients with hereditary angioedema
Intervention	Drugs in Appendix 1
Comparator	Drugs in Appendix 1
Outcomes	Morbidity, mortality, symptom severity, attack rate, quality of life, functional status
Setting	Outpatient

Appendix 5: Prior Authorization Criteria

Hereditary Angioedema

Goal(s):

- To promote safe and effective use of hereditary angioedema treatments.

Length of Authorization:

- Up to 12 months

Requires PA:

- All pharmacotherapy for hereditary angioedema (pharmacy and physician administered claims).

  NOTE: This policy does not apply to hereditary angioedema treatments administered during emergency department visits or hospitalization.

Covered Alternatives:

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

Table 1. FDA Approved indications and dosing for hereditary angioedema treatments

Drug Name	Place in Therapy	FDA Indication(s)	Dose and Frequency
C1 esterase inhibitor (Berinert®)	Acute	Abdominal, facial, or laryngeal attacks	20 units/kg intravenously as a single dose
C1 esterase inhibitor, recombinant (Ruconest®)	Acute	Attacks in adults and adolescents. Efficacy has not been established in laryngeal attacks.	50 units/kg intravenously as a single dose; maximum dose: 4,200 units; may repeat once within 24 hours if attack continues

Ecallantide (Kalbitor®)	Acute	Attacks in patients ≥12 years of age	30 mg as a one-time dose (3 subcutaneous injections); may repeat once within 24 hours if attack continues
Icatibant (Firazyr®)	Acute	Attacks in adults ≥18 years of age	30 mg injection once; may repeat every 6 hours if response is inadequate; maximum dose per day: 90 mg
C1 esterase inhibitor (Cinryze®)	Prophylaxis	HAE prophylaxis in patients ≥6 years of age	1,000 units intravenously every 3 to 4 days (twice weekly); doses up to 2,500 units (≤100 units/kg) every 3 or 4 days may be considered based on individual patient response.
C1 esterase inhibitor (Haegarda®)	Prophylaxis	HAE prophylaxis in ~~adults and adolescents~~patients ≥6 years of age	60 units/kg subcutaneous every 3 to 4 days (twice weekly)
Berotralstat (Orladayo™)	Prophylaxis	HAE prophylaxis in patients ≥12 years of age	110 mg or 150 mg orally daily
Lanadelumab-flyo (Takhzyro™)	Prophylaxis	HAE prophylaxis in patients ≥12 years of age	300 mg subcutaneous injection every 2 weeks; may consider dosing every 4 weeks for patients who are well-controlled for > 6 months

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this a request for continuation of prophylactic therapy OR for treatment of a second acute attack previously approved through fee-for-service?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #3
3. Is the request for an FDA approved indication and place in therapy according to **Table 1** and is there confirmed laboratory diagnosis of hereditary angioedema (e.g., low C4 levels and either low C1 inhibitor antigenic levels or low C1 inhibitor functional levels)?	**Yes**: Go to #4 Document labs	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the diagnosis funded by OHP?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; not funded by the OHP.

Approval Criteria		
5. Has the provider documented discussion with the patient of risks (including thrombotic events and/or anaphylaxis) versus benefits of therapy?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness. Notify provider of potential serious adverse effects of therapy. See notes below.
6. Is the request for a C1 esterase inhibitor or ecallantide ~~icatibant or lanadelumab-flyo~~?	**Yes:** Go to #~~7~~8	**No:** Go to #8~~7~~
7. Is the patient prescribed concurrent epinephrine or do they have epinephrine on hand?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness.
8. Is the medication intended to be administered by a non-healthcare professional (e.g., self-administered)?	**Yes:** Go to #9	**No:** Go to #10
9. Has the member received training on identification of an acute attack?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness.
10. Is the request for treatment of an acute hereditary angioedema attack?	**Yes:** Go to #13 Document attack severity if available	**No:** Go to #11
11. Is the request for prophylactic use in a patient with a history of hereditary angioedema attacks?	**Yes:** Go to #12 Document baseline number of attacks in the last 6 months	**No:** Pass to RPh. Deny; medical appropriateness.
12. Have potential triggering factors for angioedema including medications such as estrogens, progestins, or angiotensin converting enzyme inhibitors been assessed and discontinued when appropriate?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
13. Will the prescriber consider a change to a preferred product? Message: Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Approve for the following recommended durations: Acute treatment: Approve based on standard FDA dosing for treatment of a single acute attack (see **Table 1**) Prophylactic treatment: Approve for up to 6 months or length of therapy, whichever is less.

Renewal Criteria		
1. Is the request for additional treatment for acute attacks?	**Yes:** Go to #2	**No:** Go to #5
2. Is there documented utilization and benefit of the initial approved dose?	**Yes:** Approve based on standard FDA dosing for treatment of a single acute attack (see **Table 1**). Document attack severity if available	**No:** Go to #3
3. Does the patient currently already have at least one on-demand dose for an acute attack?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #4

Renewal Criteria		
4. Is there documentation from the prescriber that an on-demand dose is necessary and risks of therapy continue to outweigh the benefits?	**Yes:** Approve based on standard FDA dosing for treatment of a single acute attack (see **Table 1**). Document attack severity if available	**No:** Pass to RPh. Deny; medical appropriateness.
5. Since initiation of therapy, has the number or severity of hereditary angioedema attacks decreased?	**Yes:** Go to #6 Document change in attack frequency or severity	**No:** Pass to RPh. Deny; medical appropriateness.
6. Has the patient been attack free for at least 6 months?	**Yes:** Go to #7	**No:** Approve for up to 12 months.
7. Is there documentation from the prescriber that they have evaluated continued necessity of long-term prophylactic treatment at the current dose?	**Yes:** Approve for up to 6 months.	**No:** Pass to RPh. Deny; medical appropriateness.

Notes on adverse effects of treatment:

Berotralstat

- Doses above 150 mg daily have been associated with QT prolongation. Dose adjustment is recommended for patients with moderate to severe hepatic impairment or with concomitant p-glycoprotein or BCRP inhibitors. Avoid use with p-glycoprotein inducers.

C1 esterase inhibitors

- In clinical trials of patients with moderate to severe hereditary angioedema attacks, use of C1 esterase inhibitors improved the duration of symptoms by an average 1-2 hours compared to placebo. Prophylactic use has only been evaluated in patients with more than 2 attacks per month.
- Hypersensitivity reactions have been observed with C1 esterase inhibitors. Due to the risk of anaphylaxis, it is recommended that all patients prescribed human derived C1 esterase inhibitors have epinephrine immediately available.
- Serious arterial and venous thrombotic events have been reported with use of C1 esterase inhibitors, particularly in patients with pre-existing risk factors for thromboembolism. The exact incidence of thrombosis with C1 esterase inhibitors is unclear. In patients using prophylactic therapy with Cinryze®, over an average of 2.6 years, 3% of patients experienced thrombosis.

Ecallantide

- The average improvement in symptoms compared to placebo at 4 hours after treatment of an acute attack was 0.4 points on a 0-3 point scale.

- Ecallantide has a box warning for anaphylaxis. In clinical trials, 3-4% of patients treated with ecallantide experienced anaphylaxis. Risks of treatment should be weighed against the benefits.

Icatibant

- In clinical trials of icatibant for acute attacks, time to 50% overall symptom improvement was 17.8 hours better than placebo (19 vs. 2 hours). A second study demonstrated no difference from placebo in time to symptom improvement. There are no data available on quality of life, daily activities, physical or mental functioning with use of icatibant.

Lanadelumab-flyo

- Prophylactic use has only been evaluated in patients with more than 1 moderate-severe attack per month. Hypersensitivity reactions were observed in 1% of patients treated with C1 esterase inhibitors. Elevated liver enzymes were also observed more frequently with lanadelumab compared to placebo (2% vs. 0%), and the long-term safety is unknown.

P&T/DUR Review: 6/21 (SS); 3/19 (SS)
Implementation: TBD; 5/1/19

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Drug Class Update with New Drug Evaluations: Multiple Sclerosis

Date of Review: June 2021

Date of Last Review: August 2020
Dates of Literature Search: 02/03/2020 – 03/01/2021

Generic Name: Ofatumumab
Ponesimod

Brand Name (Manufacturer):
Kesimpta (Novartis)
Ponvory (Janssen)
Dossier Received: yes, for ofatumumab

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

Purpose for Class Update:
Evidence for the comparative effectiveness of disease modifying drugs (DMDs) for multiple sclerosis (MS) was last reviewed by the Oregon Pharmacy & Therapeutic Committee (P&T) in August 2020 as summarized in a Drug Effectiveness Review Project (DERP) report. This review examines new comparative evidence of DMDs for MS published since 2020 and summarizes the evidence for 2 new DMDs, ofatumumab and ponesimod, approved to treat relapsing forms of MS.

Research Questions:
1. What is the comparative effectiveness and efficacy of DMDs for MS?
2. Do DMDs for MS differ in harms?
3. Are there subgroups of patients with MS based on demographics (age, racial or ethnic groups, and gender), socioeconomic status, concomitant medications, severity of disease, or co-morbidities for which one DMD is more effective or associated with fewer adverse events?
4. What is the evidence for efficacy and safety for use of ofatumumab in relapsing MS?
5. What is the evidence for efficacy and safety of ponesimod in relapsing MS ?

Author: Deanna Moretz, PharmD, BCPS

Conclusions:

Multiple Sclerosis Disease-Modifying Drugs

- No new evidence of comparative efficacy or effectiveness of DMDs approved to treat MS has been published since the last MS class review.
- A moderate-quality systemic review and meta-analysis evaluated the prevalence of alemtuzumab-induced autoimmune thyroid events (ATEs) in patients with MS.[1] A 33% prevalence of newly diagnosed ATEs was recorded in 1362 MS patients treated with alemtuzumab.[1] Among all ATEs, Graves' disease was the most represented (63% of cases), followed by Hashimoto thyroiditis (15% of cases).[1]
- The National Institute for Health and Clinical Excellence (NICE) updated guidelines for alemtuzumab in treatment of patients with relapsing-remitting multiple sclerosis (RRMS). The main disadvantages of alemtuzumab treatment are the possible serious adverse effects observed during the trials, including idiopathic thrombocytopenic purpura, kidney disease or failure, thyroid disease and death.[2] While alemtuzumab's marketing authorization permits its use as a first-line treatment, it is more likely to be offered to people for whom other disease-modifying treatments have not been effective.[2]
- NICE guidance recommends ocrelizumab as an option for treating early primary progressive multiple sclerosis (PPMS) with imaging features characteristic of inflammatory activity in adults.[3]
- NICE guidance for cladribine, peginterferon, and siponimod for treatment of RRMS was recently issued. Cladribine is recommended as an option for treating rapidly evolving severe RRMS in adults.[4] Peginterferon beta-1a is recommended as an option for treating RRMS in adults.[5] Siponimod is recommended as an option for treating Secondary Progressive Multiple Sclerosis (SPMS) with evidence of active disease (that is, relapses or imaging features of inflammatory activity) in adults.[6]
- The Canadian Agency for Drugs and Technologies in Health (CADTH) recommends siponimod for the treatment of patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features characteristic of MS inflammatory activity, to delay the progression of physical disability, only if specific conditions are met.[7]
- There is insufficient evidence to address the role of DMDs in managing specific subpopulations of persons with MS.

Ofatumumab

- Ofatumumab (Kesimpta™) is a recombinant human monoclonal antibody that binds CD20 expressed on B lymphocytes. The safety and efficacy of ofatumumab in patients with relapsing forms of MS were evaluated in 2, identically designed, phase 3 trials; ASCLEPIOS I and ASCLEPIOS II.[8] The trials were multicenter, double-blind, randomized, active comparator-controlled studies conducted in parallel for up to 30 months.[8]
- In both trials, moderate-quality evidence showed ofatumumab significantly improved the adjusted annualized relapse rate compared with teriflunomide in ASCLEPIOS I (0.11 vs. 0.22, respectively; difference -0.11; 95% confidence interval [CI], -0.16 to -0.06; P<0.001) and in ASCLEPIOS II (0.10 vs. 0.25, respectively; difference -0.15; 95% CI, -0.20 to -0.09; P<0.001).[8] In pooled analysis of both trials, the percentage of patients with confirmed worsening disability was significantly reduced with ofatumumab compared with teriflunomide at 3 months based on moderate-quality evidence [10.9% ofatumumab vs. 15.0% teriflunomide; hazard ratio (HR) 0.66; P=0.002; number need to treat (NNT) 25]; and at 6 months (8.1% vs. 12.0%; HR 0.68; P=0.01; NNT 26).[8]
- Adverse events that occurred in at least 10% of patients treated with ofatumumab included injection-related reactions, nasopharyngitis, headache, injection-site reaction, upper respiratory tract infection, and urinary tract infection; events that occurred in at least 10% of those treated with teriflunomide included nasopharyngitis, injection-related reactions, alopecia, upper respiratory tract infection, headache, and diarrhea.[8] Ofatumumab is contraindicated in patients with active hepatitis B virus infection.[9]

Ponesimod

- Ponesimod is a selective, second-generation, sphingosine 1-phosphate receptor 1 ($S1PR_1$) modulator. The safety and efficacy of ponesimod in patients with relapsing MS were evaluated in a multicenter, double-blind, active-comparator, phase 3 superiority randomized controlled trial; OPTIMUM.[10]
- In the OPTIMUM trial, patients with RRMS or SPMS (n=1133) were randomized 1:1 to ponesimod 20 mg starting on day 15 or teriflunomide 14 mg once daily for 108 weeks. The primary endpoint was the annualized relapse rate. Impact on disability accumulation over 12 and 24 weeks were key secondary endpoints. Compared with teriflunomide, moderate-quality evidence showed ponesimod reduced the mean annualized relapse rate over 2 years (mean annualized relapse rate with teriflunomide, 0.290 vs. 0.202 with ponesimod; rate ratio, 0.695; 99% CI, 0.536-0.902; P<0.001).[10] Moderate-quality evidence showed the risk of 12-week confirmed disability accumulation was not statistically different between ponesimod and teriflunomide (10.1% vs. 12.4%; HR, 0.83; 95% CI, 0.58-1.18; P=0.29).[10] Similar results were observed in exploratory disability accumulation over 24 weeks (8.1% vs 9.9%; HR, 0.84; 95% CI, 0.57 to 1.24; P=0.37).[10]
- Overall, the proportion of patients who experienced at least 1 treatment-emergent adverse event (TEAE) was similar between the 2 treatment groups (ponesimod 88.8% versus teriflunomide 88.2%).[10] The most common TEAEs (≥ 10% in either group) were an increased alanine aminotransferase (ALT) level (19.5% vs. 9.4%), nasopharyngitis (19.3% vs. 16.8%), headache (11.5% vs. 72 12.7%), upper respiratory tract infection (10.6% vs. 10.4%), and alopecia (3.2% vs. 12.7%) in the ponesimod versus teriflunomide groups, respectively.[10]

Recommendations:

- Apply clinical prior authorization (PA) criteria to ofatumumab subcutaneous injection for both physician administered and point of sale pharmacy claims (**Appendix 5**). Limit use to:
    - Funded MS conditions
    - History of inadequate response to at least 2 DMDs approved for MS; and
    - Prescribed by a neurologist
- Add ponesimod tablets to the Oral MS Drug PA criteria (**Appendix 5**).
- Review comparative drug costs and Preferred Drug List (PDL) status for ofatumumab and ponesimod in Executive Session.

Summary of Prior Reviews and Current Policy

At the June 2020 P & T Committee meeting, PA changes were proposed to accommodate expanded FDA-approved indications for MS treatments until a comprehensive evidence review could be completed. Several medications for MS, which were previously approved only for relapsing-remitting disease, received expanded indications in late 2019 for all forms of relapsing MS including Clinically Isolated Syndrome (CIS), RRMS, and active SPMS. In addition, it was recommended to remove daclizumab from the PA criteria as it was voluntarily recalled from the U.S. market due to safety concerns in 2018.

At the August 2020 P & T Committee Meeting, DMDs for MS were reviewed in detail based on a report compiled by the DERP at the Oregon Health & Science University (OHSU) Center for Evidence Based Policy.[11] Five new oral MS drugs were reviewed in the 2020 class update including: diroximel fumarate, monomethyl fumarate, ozanimod, cladribine, and siponimod. Prior authorization criteria for oral MS drugs were revised to include newly approved DMDs. In addition, safety monitoring metrics and renewal criteria were added to the oral MS drugs PA criteria. Finally, PA criteria for natalizumab were revised to reflect the expanded indication for all forms of relapsing MS.

The PDL status of MS drugs is presented in **Appendix 1**. During the first quarter of 2021, 5 fee-for-service (FFS) patients had pharmacy claims processed for MS drugs. Over half of the claims were for the nonpreferred oral medications dimethyl fumarate (40%) and fingolimod (40%). The rest of the claims were for the preferred injectable interferon beta-1a (20%).

Background:
Multiple sclerosis is a chronic, immune-mediated disease of the central nervous system characterized by inflammation, demyelination, and neuronal destruction. Common neurological manifestations of multiple sclerosis include optic neuritis, diplopia, sensory loss, limb weakness, gait ataxia, loss of bladder control, and cognitive dysfunction.[12] The mean age of diagnosis is approximately 30 years, with most patients presenting with periodic neurological relapses.[12] One to two decades after onset, many patients with multiple sclerosis enter a progressive phase of the disease.[12] In 2016, it was estimated that MS affects approximately 2.2 million individuals worldwide.[12] Prevalence of MS and disability-adjusted life-years (DALYs) associated with MS were significantly higher in women than in men, and there were significant gradients in prevalence and incidence across different regions of the world.[12] North Africa, sub-Saharan Africa, Latin America, Asia, Oceania, and the Middle East have the lowest incidence of MS.[12] The populations with the highest prevalence of MS include North America, Western Europe and Australia.[12] Greater sun exposure and higher vitamin D levels are postulated to protect against MS.[12] The 2010 prevalence for MS in the U.S. was estimated at 309 people per 100,000 individuals, representing an overall estimate of 727,350 patients in the U.S. diagnosed with MS.[13] This analysis was based on health claims data from Medicare, Medicaid, the Department of Veterans affairs, and 3 private insurance datasets (Optum, Truven Health, and Kaiser Permanente).[13]

Diagnosis of MS is based on a combination of signs and symptoms, radiographic findings (e.g., magnetic resonance imaging [MRI] T2 lesions), and laboratory findings (e.g., cerebrospinal fluid–specific oligoclonal bands), which are components of the 2017 McDonald Criteria.[14] Four distinct clinical courses have been identified for MS: CIS, RRMS, SPMS, and PPMS.[15] Clinically Isolated Syndrome is an acute demyelinating episode lasting greater than 24 hours and is the first onset of MS symptoms. Most patients who present with CIS are eventually diagnosed with MS. Patients with RRMS have clearly defined relapses lasting 3 to 6 months with full recovery and minimal disease progression between symptomatic episodes. Relapsing-remitting MS may be either characterized as active or not active. About 85% of patients with MS are initially diagnosed with RRMS.[16] Secondary progressive MS begins as RRMS, but gradual worsening of neurologic symptoms is observed over time.[17] After 15 to 20 years, about 65% of RRMS patients enter the secondary progressive phase.[16] Relapsing MS includes CIS, RRMS, and active SPMS in adults. Primary Progressive MS is characterized by a steady decline in neurologic function and progressive accumulation of disability without acute attacks or relapses. Approximately 10 to 15% of MS patients have PPMS, and in contrast to RRMS, symptoms typically begin in the patients' fifth or sixth decade, a later age of onset than RRMS.[18] PPMS is distributed more equally between men and women than RRMS. The majority of available direct evidence continues to reside in patients with relapsing forms of MS rather than progressing forms of MS.

Progression of MS is assessed by the amount of disability caused by the disease. The Expanded Disability Status Scale (EDSS) was developed to provide a standardized measure of neurological impairment in MS. The EDSS ranges from 0 (normal neurologic exam) to 5 (ambulatory without aid for 200 meters) to 10 (death due to MS), with lower scores indicating more mobility and activity by the patient.[19] The EDSS is complicated to score and, at lower degrees of disability, the scale is very subjective with poor interrater and test–retest reliability.[20] In addition, it is nonlinear over its range in comparison with the actual level of function and it places a much greater emphasis on ambulation status than other neurologic functions.[19] Despite these limitations, the EDSS continues to be the standard disability measure for MS clinical research. Clinical trials have defined disability progression when assessed over 3 to 6 months as an increase in EDSS of 0.5 points when the score is between 5.6 to 8.5 and 1.0 point when the score is between 0 and 5.50.[21] Some researchers have proposed that longer trials (with duration of at least 1 year) with greater changes in the EDSS scores (greater than 1-2 points) may better identify patients with sustained disability.[22]

The annualized relapse rate is often included as an outcome measure for MS clinical trials because it is easy to quantify. Relapses are generally defined as neurologic symptoms lasting more than 24 hours which occur at least 30 days after the onset of a preceding event.[21] However, the probability of relapse is not a consistent function over time. Patients are usually enrolled in a trial at the time of MS diagnosis when the probability for relapses is high, and as time progresses, this probability decreases.[21] In order to have enough power to detect a significant reduction in relapses, research suggests a clinical trial needs to last at least 1 year, but this measure may also be less meaningful than evaluating the total number of relapses over a longer period of time.[23] In addition, due to low relapse rates recorded in recent trials, the sample size required for new studies may not be feasible.[23] In addition to clinical measures, radiographic measures of disease progression include the development of new T2 lesions, enlarging T2 lesions, or both.[14]

The FSIQ-RMS is a validated patient-reported outcome measure that was recently developed by Actelion Pharmaceuticals to evaluate fatigue-related symptoms and the impacts of those symptoms on the lives of people with relapsing MS.[24] An electronic questionnaire consisting of 7 items included in the fatigue-related symptom domains is administered daily over 7 days.[10] The total score for each domain is standardized onto a scale of 0 to 100 with higher scores indicating more fatigue.[10] A reduction of 6.3 points was considered a meaningful change threshold in the phase 3 ponesimod trial.[10]

Treatment of MS falls into three main categories: treatment of acute attacks, symptomatic therapy to improve the patient's quality of life, and treatment with DMDs to alter the natural course of the disease and reduce progressive disability over time. Acute relapses are treated with high-dose systemic corticosteroids for 3 to 5 days. Specific symptoms including spasticity, pain, bladder dysfunction, fatigue, and mood dysregulation are treated accordingly with appropriate agents. Early use of DMDs in patients with relapsing forms of MS has been shown to reduce the frequency of relapses, lessen severity of relapses, and slow progression of disability.[25] All DMDs modulate the immune system through various mechanisms that include sequestration of lymphocytes, interference with DNA synthesis in lymphocytes, depletion of immune cells, and/or changes in cytokine secretion pattern.[14] The FDA-approved DMDs for MS include interferons, glatiramer acetate, teriflunomide, sphingosine 1-phosphate receptor modulators, fumarates, cladribine, and 4 types of monoclonal antibodies. Efficacy rates of DMDs, defined by reduction in annualized relapse rates compared with placebo or active comparators, range from 29% to 68%.[14]

There are 2 main treatment approaches for relapsing MS that are based on evaluating the risks and efficacy of DMDs.[14] The escalation approach starts with the least-potent medications with relatively few adverse effects, such as interferons or fumarates, and if there is evidence of disease activity the treatment is escalated to a more potent medication.[14] This approach minimizes risks but may result in undertreatment, defined as breakthrough disease and accumulated disability.[14] An alternative option is to initiate a medication with higher potency, such as ocrelizumab or natalizumab, at the time of diagnosis.[14] The rationale for this treatment approach is to provide better relapse control and delay accumulation of disability.[14] A limitation of this approach is that patients are exposed to higher risks of adverse events and some patients may not require such intensive treatment.[14] Information about the DMDs that have been FDA-approved for the treatment of MS is presented in **Table 1**.

Table 1: FDA-Approved Disease-Modifying Drugs used to manage Multiple Sclerosis[26,27]

Generic Name	Brand Name	Dose/Route/Frequency	FDA Indication	REMS Program	Major Safety Concerns	Monitoring
ORAL AGENTS						
Sphingosine 1-Phosphate Receptor Modulators						
Fingolimod (Affects $S1PR_1$, $S1PR_3$, $S1PR_4$, & $S1PR_5$)	GILENYA	≥ 40 kg: 0.5 mg PO once daily < 40 kg: 0.25 mg PO once daily	CIS RRMS SPMS **Approved for patients ≥10 years of age**	No	Infections, PML, bradycardia with first dose, hepatotoxicity hypertension, teratogenicity, and macular edema	Cardiac monitoring with the first dose. Ophthalmic screening at baseline and 3-4 months after starting therapy. LFTs and CBC every 6 months.
Siponimod (Affects $S1PR_1$ & $S1PR_5$)	MAYZENT	2 mg PO once daily (maintenance) 1 mg PO once daily for patients with CYP2C9*1/*3 OR *2/*3 genotype	CIS RRMS SPMS	No	Infections, PML, bradycardia, AV conduction delays, hepatotoxicity, macular edema, hypertension, teratogenicity	CYP2C9 genotype determination before treatment initiation. CBC and LFTs every 6 months. Ophthalmic screening and ECG at baseline.
Ozanimod (Affects $S1PR_1$ & $S1PR_5$)	ZEPOSIA	0.92 mg PO once daily (maintenance)	CIS RRMS SPMS	No	Infections, PML, bradyarrhythmia, AV conduction delays, hepatotoxicity, hypertension, macular edema, teratogenicity	CBC and LFTs at baseline and every 6 months. Ophthalmic screening and ECG at baseline.
Ponesimod (Affects $S1PR_1$)	PONVORY	20 mg PO once daily (maintenance)	CIS RRMS SPMS	No	Infections, PML, bradyarrhythmia, AV conduction delays, hepatotoxicity, hypertension, macular edema, teratogenicity	CBC and LFTs every 6 months. Ophthalmic screening and ECG at baseline.
Fumarates						
Dimethyl Fumarate	TECFIDERA	240 mg PO twice a day (maintenance)	CIS RRMS SPMS	No	Infections, lymphopenia, PML, and hepatotoxicity	CBC with lymphocyte count and LFTs every 6 months
Monomethyl Fumarate	BAFIERTAM	190 mg PO twice daily (maintenance)	CIS RRMS SPMS	No	Infections, lymphopenia, PML, and hepatotoxicity	CBC with lymphocyte count and LFTs every 6 months
Diroximel Fumarate	VUMERITY	462 mg PO twice daily (maintenance)	CIS RRMS SPMS	No	Infections, lymphopenia, PML, and hepatotoxicity	CBC with lymphocyte count and LFTs every 6 months
Others						

Teriflunomide	AUBAGIO	7 mg or 14 mg PO once daily	CIS RRMS SPMS	No	Black Box Warnings: Hepatotoxicity and Teratogenicity Other Warnings: infections and hypertension	CBC, LFTs, and blood pressure every 6 months
Cladribine	MAVENCLAD	Cumulative dose of 3.5 mg/kg PO divided into 2 yearly treatment courses (1.75 mg/kg per treatment course).	RRMS SPMS	No	Black Box Warnings: Malignancies and Teratogenicity Other Warnings: Bone marrow suppression, PML, lymphopenia, infections, cardiac failure, and hepatoxicity **Due to its safety profile, cladribine is recommended for patients who have had an inadequate response to, or who are unable to tolerate an alternative MS treatment**	CBC with lymphocyte count and LFTs every 6 months
INJECTABLE AGENTS						
Interferons						
Interferon beta-1a	AVONEX	30 mcg IM once weekly (maintenance)	CIS RRMS SPMS	No	Hepatotoxicity, thrombocytopenia, increased risk of spontaneous abortion, depression, and suicidal ideation	Thyroid function, CBC and LFTs every 6 months
Interferon beta-1a	REBIF	22 or 44 mcg SC three times a week				
Peginterferon beta-1a	PLEGRIDY	125 mcg SC every 14 days				
Interferon beta-1b	BETASERON, EXTAVIA	250 mcg SC every other day				
Monoclonal Antibodies						
Alemtuzumab	LEMTRADA	Intravenous infusion for 2 treatment courses. First course: 12 mg IV over 4 hours once a day for 5 consecutive days (total 60 mg). Second course: 12 mg once a day for 3 days (total 36 mg). Begin 12 months after the first treatment course.	RRMS SPMS	Yes	Black Box Warnings: Autoimmunity, Infusion Reactions, Stroke, and Malignancies Other Warnings: Infections, PML, thyroid autoimmunity, glomerular nephropathies, thrombocytopenia, autoimmune hepatitis **Due to safety profile, reserve for patients who have inadequate response to 2 or more MS drugs**	Thyroid function every 3 months. CBC with differential, serum creatinine, and urinalysis every month. Baseline and yearly LFTs and skin exams.

Natalizumab	TYSABRI	300 mg via IV infusion every 4 weeks	CIS RRMS SPMS	Yes	Black Box Warnings: PML Other Warnings: infections, hypersensitivity, teratogenicity, thrombocytopenia, hepatotoxicity **consider risk of PML vs. benefit of therapy**	JCV antibody testing and brain MRI every 6 months. CBC and LFTs every 6 months
Ocrelizumab	OCREVUS	600 mg IV every 6 months (maintenance)	CIS RRMS SPMS PPMS	No	Infusion reactions, infections and PML	Hepatitis B virus screening prior to starting therapy
Ofatumumab	KESIMPTA	20 mg SC every 4 weeks	CIS RRMS SPMS	No	Infusion reactions and infections	Hepatitis B virus screening prior to starting therapy
Others						
Mitoxantrone	NOVANTRONE	12 mg/m^2 IV infusion every 3 months – duration of therapy limited to 2 years and cumulative dose of 140 mg/m^2	RRMS SPMS	No	Black Box Warning: Dose-related Cardiotoxicity **Considered as last resort treatment for patients that have failed other therapies**	ECG and LVEF before each infusion. CBC and LFTs every 6 months
Glatiramer Acetate	COPAXONE, GLATOPA	20 mg SC once daily; OR 40 mg SC three times a week	CIS RRMS SPMS	No	Transient post injection reactions (chest pain, dyspnea, tachycardia, anxiety, palpitations, flushing, urticaria) and hepatoxicity	None required
Abbreviations: AML = acute myeloid leukemia; CBC = complete blood count; CIS = clinically isolated syndrome; ECG = electrocardiogram; FDA = U.S. Food and Drug Administration; IM = Intramuscular; IV = Intravenous; JCV = John Cunningham Virus; LFTs = liver function tests; LVEF= left ventricular ejection fraction; MS = multiple sclerosis; MRI = magnetic resonance imaging; PO = Oral; PPMS = primary progressive multiple sclerosis; PML = progressive multifocal leukoencephalopathy; REMS = Restricted Evaluation and Mitigation Strategy; RRMS = relapsing-remitting multiple sclerosis; SC= Subcutaneous, S1PR = sphingosine 1-phosphate receptor; SPMS = secondary progressive multiple sclerosis						

Methods:

A Medline literature search for new systematic reviews and 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 DERP, Agency for Healthcare Research and Quality (AHRQ), NICE, Department of Veterans Affairs, and the 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:

Alemtuzumab-Induced Thyroid Events in Multiple Sclerosis

The overall prevalence of ATEs after alemtuzumab is estimated to range from 34% to 41%, with Graves' disease appearing to be the leading thyroid event.[1] The purpose of a 2020 moderate-quality systemic review and meta-analysis was to evaluate evidence on prevalence of the spectrum of alemtuzumab-induced ATEs in patients with MS.[1] Literature on this topic was searched through July 2019. Studies that described alemtuzumab treatment in other disease states (e.g. chronic lymphocytic leukemia, rheumatoid arthritis, stem cell transplantation, and kidney transplantation) were excluded.[1] Case reports, reviews, editorials, letters, commentaries, and meeting abstracts were excluded from the analysis.[1] Seven studies reporting ATEs in MS patients treated with alemtuzumab were identfied.[1] Four RCTs, 2 observational studies, and 1 case series met inclusion criteria.[1] Overall, risk of bias for these studies was rated as low to unclear. Selection bias due to unclear allocation concealment and randomization contributed to unclear bias assessments for the RCTs.[1] Detection and reporting biases were rated as low risk of bias for all 7 studies.[1]

Among the overall pooled number of 1362 MS patients treated with alemtuzumab, a 33% prevalence of newly diagnosed ATEs was recorded.[1] Among all ATEs, Graves' disease was the most represented (63% of cases), followed by Hashimoto thyroiditis (15% of cases).[1] Of all patients with Grave's disease, 12% likely had spontaneous remission, 56% required only anti-thyroid drugs, 22% needed additional radioiodine, and 11% underwent definitive surgery.[1] The authors concluded among different categories of ATEs, Graves' hyperthyroidism was the most common thyroid dysfunction associated with alemtuzumab administration in MS patients, occurring in more than half of cases.[1]

After review, 3 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses), wrong study design of included trials (e.g., observational),[28] comparator (e.g., no control or placebo-controlled),[29] or outcome studied (e.g., non-clinical).[30]

New Guidelines:

High Quality Guidelines:

National Institute for Health and Clinical Excellence

Since the last MS class review, NICE updated guidelines for alemtuzumab for treatment of RRMS. New guidance was also published for ocrelizumab for treatment of PPMS, and for cladribine, peginterferon, and siponimod for treatment of RRMS. NICE guidance for each of these drugs is summarized below.

Alemtuzumab for Treating Highly Active Relapsing-Remitting Multiple Sclerosis

In 2020, the NICE Appraisal Committee reviewed warnings and precautions associated with alemtuzumab based on a safety review from the European Medicine Agency (EMA). For people with active RRMS eligible for treatment under the Association for British Neurologists' guidelines, alemtuzumab should be considered as a first-line treatment option, alongside beta interferons or glatiramer acetate.[2] While alemtuzumab's United Kingdom marketing authorization permits its use as a first-line treatment, it is more likely to be offered to people for whom other DMDs have not been effective.[2] The primary disadvantages of alemtuzumab are possible serious adverse effects observed during the trials, including idiopathic thrombocytopenic purpura, kidney disease or failure, thyroid disease and death.[2] Thyroid disease is the most common complication, affecting one-third of patients with MS treated with alemtuzumab.[2] The primary advantages of alemtuzumab include high efficacy, lack of flu-like symptoms associated with beta interferons, and able to be used in pregnancy.[2] Alemtuzumab NICE guidance was updated in March 2020.

- Alemtuzumab is recommended as an option for treating highly active RRMS in adults with:
    - highly active disease despite a full and adequate course of treatment with at least 1 DMD; or

- rapidly-evolving severe RRMS defined by 2 or more disabling relapses in 1 year, and with 1 or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load compared with a previous MRI.[2]

Ocrelizumab for Treating Primary Progressive Multiple Sclerosis

New NICE guidance for the use of ocrelizumab to treat PPMS was published June 2019. There are currently no DMDs available for PPMS.[3] Results of one clinical trial show that ocrelizumab can slow the worsening of disability in patients with PPMS, although the size and duration of this effect are uncertain.[3] Given the unmet clinical need, the most plausible cost-effectiveness estimates for ocrelizumab at the agreed price compared with best supportive care alone are within the range that NICE considers an acceptable use of National Health Service (NHS) resources.[3]

- Ocrelizumab is recommended as an option for treating early PPMS with imaging features characteristic of inflammatory activity in adults.[3]

Peginterferon Beta-1a for Treating Relapsing–Remitting Multiple Sclerosis

NICE issued updated guidance for the use of peginterferon for treatment of RRMS in February 2020. Clinical trials show that peginterferon beta-1a slows disease progression and reduces the frequency of relapses when compared with placebo in patients with RRMS.[5] There is also an indirect comparison suggesting that there are no differences in effectiveness when comparing peginterferon beta-1a with other beta interferons and glatiramer acetate. [5] However, it involves less frequent injections than other beta interferons, and offers an additional choice for people with RRMS.[5]

- Peginterferon beta-1a is recommended as an option for treating RRMS in adults.[5]

Cladribine for Treating Relapsing–Remitting Multiple Sclerosis

NICE issued new guidance for the use of cladribine in management of RRMS in December 2019. Highly active RRMS is currently treated with alemtuzumab, fingolimod or natalizumab.[4] Clinical trials show that cladribine tablets reduce relapses and slow the progression of disability compared with placebo for people with RRMS.[4] The effectiveness of cladribine for treating rapidly evolving, severe, or suboptimally treated RRMS is not proven, but it is likely to be more effective than placebo.[4] Based on indirect analyses, there is not enough evidence to determine whether cladribine is more or less effective than other treatments for people with rapidly evolving severe and suboptimally treated multiple sclerosis.[4] Because of this, cladribine and alternative treatments are considered equally effective by NICE.[4] Cladribine is less costly than other treatments and needs less frequent dosing and monitoring. It is cost effective compared with all other treatments, so it can be recommended for rapidly evolving, severe, and suboptimally treated RRMS.[4]

- Cladribine is recommended as an option for treating highly active MS in adults, only if the person has rapidly evolving severe RRMS, that is with at least:
  - 2 relapses in the previous year; and
  - 1 T1 gadolinium-enhancing lesion at baseline MRI or a significant increase in T2-lesion load compared with a previous MRI; or
  - RRMS that has responded inadequately to treatment Witham's, defined as 1 relapse in the previous year and MRI evidence of disease activity.[4]

Siponimod for Treating Secondary Progressive Multiple Sclerosis

NICE issued new guidance for the use of siponimod for treatment of SPMS in November 2020. Clinical trials show that siponimod reduces the number of relapses and slows disability progression in patients with SPMS compared with placebo.[6] It is uncertain how effective siponimod is compared with interferon beta-1b because there is no evidence directly comparing them.[6] The most plausible cost-effectiveness estimates for siponimod compared with interferon beta-1b are in the range that NICE normally considers an acceptable use of NHS resources.[6]

- Siponimod is recommended, as an option for treating SPMS with evidence of active disease (that is, relapses or imaging features of inflammatory activity) in adults. [6]

Canadian Agency for Drugs and Technologies in Health (CADTH)

In September 2020, the CADTH published a clinical review of siponimod for treatment of SPMS.[7] Based on the data outlined in the report, the CADTH Canadian Drug Expert Committee recommends that siponimod be reimbursed for the treatment of patients with SPMS with active disease evidenced by relapses or imaging features characteristic of MS inflammatory activity, to delay the progression of physical disability, only if the following conditions are met:

- Patients who have all of the following characteristics:
  - History of RRMS and current active SPMS;
  - EDSS score of 3.0 to 6.5; and
  - Documented EDSS progression during the 2 years prior to initiating treatment with siponimod (≥ 1 point if EDSS < 6.0; ≥ 0.5 points if EDSS ≥ 6.0 at screening).[7]
- Siponimod should not be used in combination with other DMDs used to treat MS.

CADTH Renewal Criteria for Siponimod:

- Patients should be assessed for a response to siponimod every 6 months.
- Siponimod may be renewed for patients who do not exhibit evidence of disease progression since the previous assessment.
  - Disease progression is defined as an increase in the EDSS score of ≥ 1 point if the EDSS score was 3.0 to 5.0 at siponimod initiation, or an increase of ≥ 0.5 points if the EDSS score was 5.5 to 6.5 at siponimod initiation.[7]

CADTH Discontinuation Criteria for Siponimod:

- Treatment with siponimod should be discontinued in patients who exhibit either of the following:
  - Progression to an EDSS score of equal to or greater than 7.0 at any time during siponimod treatment; or
  - Confirmed worsening of at least 20% on the timed 25-foot walk since initiating siponimod treatment.[7]

Additional Guidelines for Clinical Context: After review, no guidelines were excluded due to poor quality.

New FDA Safety Alerts:

Table 2. Description of New FDA Safety Alerts[31,32]

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Natalizumab	TYSABRI	06/2020	Boxed Warning, Warnings and Precautions	Three factors that are known to increase the risk of PML in TYSABRI-treated patients have been identified: • The presence of anti-JCV antibodies. Patients who are anti-JCV antibody positive have a higher risk for developing PML. • Longer treatment duration, especially beyond 2 years. • Prior treatment with an immunosuppressant (e.g., mitoxantrone, azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil).

				These factors should be considered in the context of expected benefit when initiating and continuing treatment with TYSABRI.[31] Cases of thrombocytopenia, including immune thrombocytopenic purpura (ITP), have been reported with the use of TYSABRI in the post marketing setting. Symptoms of thrombocytopenia may include easy bruising, abnormal bleeding, and petechiae. Delay in the diagnosis and treatment of thrombocytopenia may lead to serious and life-threatening sequelae. If thrombocytopenia is suspected, TYSABRI should be discontinued.[31]
Glatiramer	COPAXONE GLATOPA	07/2020	Warnings and Precautions	Cases of hepatic injury, some severe, including liver failure and hepatitis with jaundice, have been reported with COPAXONE. Hepatic injury has occurred from days to years after initiating treatment with COPAXONE. If signs or symptoms of liver dysfunction occur, consider discontinuation of COPAXONE.[32]

Randomized Controlled Trials:

A total of 49 citations were manually reviewed from the initial literature search. After further review, 48 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 **Table 3** below. The full abstract is included in **Appendix 2**.

Table 3. Description of Randomized Comparative Clinical Trial

<table>
<tr><th>Study</th><th>Comparison</th><th>Population</th><th>Primary Outcome</th><th>Results</th></tr>
<tr><td>Cheshmavar M, et al.[33]

OL RCT</td><td>1. Rituximab 1 gm IV q6 months

2. Glatiramer 40 mg SC 3 times a week</td><td>Adults aged 18 to 55 years with SPMS with an EDSS 0 to 5

N=84</td><td>Comparison of EDSS between groups after 12 months of treatment</td><td>
<table>
<tr><th></th><th>Rituximab (n=43)</th><th>Glatiramer (n=41)</th><th>p-value (ITT analysis)</th></tr>
<tr><td>Baseline EDSS</td><td>3.09</td><td>3.22</td><td></td></tr>
<tr><td>EDSS at 12 months</td><td>4.02</td><td>4.60</td><td>0.179
Confidence Interval Not Reported</td></tr>
</table>
</td></tr>
<tr><td colspan="5">Abbreviations: EDSS=Expanded Disability Status Scale; ITT= Intention to Treat; IV=Intravenous; OL=open label; RCT=randomized clinical trial; SC=subcutaneous; SPMS=Secondary Progressive Multiple Sclerosis</td></tr>
</table>

NEW DRUG EVALUATION: Ofatumumab

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:

Ofatumumab (Kesimpta™) is a recombinant human monoclonal antibody that binds CD20 expressed on B lymphocytes, which results in antibody-dependent cellular cytolysis and complement-mediated lysis of B cells.[9] Ofatumumab received initial FDA approval in 2009 under the brand name Arzerra™ for treatment of patients with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab.[34] In August 2020, ofatumumab received FDA-approval for the treatment of relapsing forms of MS (e.g., CIS, RRMS, SPMS).[9] Anti-CD20 monoclonal antibodies that induce B-cell depletion, such as rituximab and ocrelizumab, have been used as DMDs for MS.[8] These drugs are administered via intravenous infusion in a clinical setting. In contrast, ofatumumab can be administered subcutaneously (SC) by the patient at home after initial doses are given under medical supervision.[8]

The safety and efficacy of ofatumumab in patients with relapsing forms of MS were evaluated in 2 identically designed phase 3 trials: ASCLEPIOS I and ASCLEPIOS II.[8] Both trials were multicenter, randomized, double-blind, double-dummy, active comparator-controlled studies conducted in parallel for up to 30 months.[8] Adult patients with RRMS or active SPMS and an EDSS of 0 to 5.5 were recruited for both studies. A total of 1,882 patients were enrolled in ASCLEPIOS I (N=927) and ASCLEPIOS II (N=955).[8] Teriflunomide 14 mg was administered orally once daily as the active comparator. Teriflunomide, an oral inhibitor of pyrimidine synthesis, reduces T-cell and B-cell activation. Loading doses of ofatumumab 20 mg were administered SC once weekly at Week 0, 1, and 2. Maintenance doses of ofatumumab 20 mg were administered SC once monthly starting at Week 4. Oral placebo capsules and placebo injections were administered in the appropriate groups to maintain blinding to the study drug by patients and investigators.

The primary end point for both trials was the annualized relapse rate. The median time in each trial was 1.5 years in ASCLEPIOS I and 1.6 years in ASCLEPIOS II.[8] A relapse was defined as the appearance of a new neurological abnormality or worsening of a previously stable pre-existing neurological abnormality.[8] A confirmed relapse was defined as a relapse accompanied by a clinically relevant change in the EDSS performed by the independent EDSS rater (i.e., an increase of at least 0.5 points on the EDSS score, or an increase of 1.0 point on two functional scores compared to the previously available rating that did not occur during a relapse).[8] Key secondary end points included disability worsening confirmed at 3 months or 6 months, disability improvement confirmed at 6 months, the number of gadolinium-enhancing lesions per T1-weighted magnetic resonance imaging (MRI) scan, and the annualized rate of new or enlarging lesions on T2-weighted MRI.[8]

In both trials, ofatumumab improved the adjusted annualized relapse rate compared with teriflunomide in ASCLEPIOS I (0.11 vs. 0.22, respectively; difference -0.11; 95% CI, -0.16 to -0.06; P<0.001) and in ASCLEPIOS II (0.10 vs. 0.25, respectively; difference -0.15; 95% CI, -0.20 to -0.09; P<0.001).[8] In the pooled analysis, the percentage of patients with confirmed disability worsening was reduced with ofatumumab compared with teriflunomide at 3 months (10.9% ofatumumab vs. 15.0% teriflunomide; HR 0.66; P=0.002; 95% CI, 0.50 to 0.86); and 6 months (8.1% ofatumumab vs. 12.0% teriflunomide; HR 0.68; P=0.01; 95% CI, 0.50 to 0.92).[32] No significant difference between groups was observed on confirmed disability improvement at 6 months (11.0% ofatumumab vs. 8.1% teriflunomide; HR 1.35; P=0.09; 95% CI, 0.95 to 1.92).[8]

Ofatumumab was also superior to teriflunomide in suppressing lesion activity on MRI.[8] In ASCLEPIOS I, the number of gadolinium-enhancing lesions per T1-weighted MRI scan was significantly lower with ofatumumab compared with teriflunomide [0.01 ofatumumab and 0.45 teriflunomide (97% lower number of

lesions ofatumumab, P<0.001)]; in ASCLEPIOS II, the corresponding numbers were 0.03 and 0.51, respectively (94% lower ofatumumab, P<0.001).[8] The annualized rate of lesions on T2-weighted MRI was also significantly lower with ofatumumab compared with teriflunomide in ASCLEPIOS I [0.72 ofatumumab and 4.00 teriflunomide (82% lower number of lesions ofatumumab, P<0.001)]; corresponding values in ASCLEPIOS II were 0.64 and 4.15, respectively (85% lower ofatumumab, P<0.001).[8] Both trials are described in further detail in **Table 4** (Comparative Evidence Summary).

Trial Limitations

Lesion counts on MRI in the teriflunomide groups were higher than those previously reported in one phase 3 trial of teriflunomide as compared with placebo, which suggests either a population with more disease activity overall in the ASCLEPIOS trials, differences in the assessment methods used at the MRI analysis centers, or both.[8] In ASCLEPIOS I, more patients withdrew from the teriflunomide arm compared to ofatumumab (19% versus 10%, respectively).[8] Reasons for study withdrawal were primarily due to patient decision [n=42; (52%) in the teriflunomide arm versus n=16; (33%) in the ofatumumab arm].[8] Discontinuations due to adverse events, loss to follow up, physician decision, and protocol deviation were similar in both treatment arms. In ASCLEPIOS II, the discontinuation rate from ofatumumab and teriflunomide was similar throughout the entire trial.[8] Larger and longer trials are required to determine the long-term effect and risks of ofatumumab as compared with other DMDs, including other anti-CD20 monoclonal antibodies.[8]

Clinical Safety:

Adverse events that occurred in at least 10% of the patients treated with ofatumumab were injection-related systemic reactions, nasopharyngitis, headache, injection-site local reactions, upper respiratory tract infection, and urinary tract infection. Events that occurred in at least 10% of those treated with teriflunomide were nasopharyngitis, injection-related systemic reactions, alopecia, upper respiratory tract infection, headache, and diarrhea.[8] Serious adverse events were reported in 9.1% of the patients treated with ofatumumab and 7.9% of those treated with teriflunomide. One death occurred in the teriflunomide group (aortic dissection) during the post-treatment follow-up period.[8] Injection-related systemic reactions occurred in 21% in the ofatumumab group and in 15.0% in the teriflunomide group (placebo injections).[8] Serious infections occurred in 2.5% of patients in the ofatumumab group and 1.8% of patients in the teriflunomide group.[8]

A summary of reported adverse reactions observed with ofatumumab compared with teriflunomide is presented in **Table 2**. Animal data suggests a risk of fetal harm with ofatumumab administration.[9] The prescribing information recommends use of an effective method of contraception during ofatumumab treatment and for 6 months after discontinuation.[9]

Table 2. Adverse Reactions Observed In Patients With RMS With Ofatumumab And Teriflunomide[9]

Adverse Reactions	Ofatumumab N=946	Teriflunomide N=936
Upper Respiratory Tract Infections	39%	38%
Injection-Related Systemic Reactions (fever, headache, nausea, chills, pruitus)	21%	15%
Headache	13%	12%
Injection-Site Local Reactions	11%	6%
Urinary Tract Infection	10%	8%
Back Pain	8%	6%
Blood Immunoglobulin M Decrease	6%	2%

Look-alike / Sound-alike Error Risk Potential: No other drugs identified

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Disability Worsening at 3 and 6 months
2) Disability Improvement at 6 months
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Annualized Relapse Rate

Table 3. Pharmacology and Pharmacokinetic Properties.[9]

Parameter	
Mechanism of Action	CD20 binding on B lymphocytes
Oral Bioavailability	N/A
Distribution and Protein Binding	Volume of Distribution: 5.42 L; Protein Binding not reported
Elimination	Ofatumumab is eliminated in two ways: 1) Target-independent route as with other IgG molecules and 2) Target-mediated route that is related to binding to B-cells
Half-Life	16 days
Metabolism	Ofatumumab is a protein for which the expected metabolic pathway is degradation to small peptides and amino acids by ubiquitous proteolytic enzymes.

Abbreviations: IgG = Immunoglobulin G; L = liters; N/A = Not Applicable

Table 4. Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Hauser SL et al.[8] ASCLEPIOS I DB, AC, MC Phase 3 RCT	1. Ofatumumab 20 mg SC on days 0, 7, 14 and 28, followed by 20 mg SC every 4 weeks (plus teriflunomide-matching placebo capsule orally once daily) 2. Teriflunomide 14 mg orally once daily (plus ofatumumab-matching SC placebo injection at frequency of group 1) Duration: Variable based on when end of study criteria was met. Median Duration: 1.5 years Maximum duration: 30 months	Demographics: -Mean Age: 38 yo -Female: 69% -White: 89% -Median EDSS score: 3.0 -Type of MS RRMS: 94% SPMS: 6% -No previous DMD treatment: 40% -Previous DMD: Interferon beta: 40% Glatiramer: 25% Dimethyl fumarate: 8% Teriflunomide: 1.5% Natalizumab: 6% Key Inclusion Criteria: -Age 18-55 y -RRMS or active SPMS -EDSS 0 to 5.5 - ≥ 1 relapse in year prior to study enrollment OR 2 relapses in 2 years prior to study enrollment OR presence of a T1 Gd-enhancing lesion within year prior to study enrollment. -Neurologically stable in month prior to study enrollment. Key Exclusion Criteria: -Use of previous MS DMDs within specified time frames prior to study enrollment -	ITT: 1.465 2.462 PP: 1.416 2.376 Attrition: 1.48 (10%) 2.81 (19%)	Primary Endpoint: Adjusted annualized relapse rate at median follow up of 1.5 years 1. 0.11 2. 0.22 Difference: -0.11; 95% CI, -0.16 to -0.06; P<0.001 Secondary Endpoints: 1. Percentage of patients with worsening disability at 3 months (Kaplan-Meier estimate) 1. 11.3% 2. 15.4% HR, 0.65; 95% CI, 0.45 to 0.96; p-value NR 2. Percentage of patients with worsening disability at 6 months (Kaplan-Meier estimate) 1. 8.2% 2. 13% HR 0.61; 95% CI 0.40 to 0.93; P-value NR 3. Percentage of patients with disability improvement at 6 months (Kaplan-Meier estimate) 1. 9.7% 2. 8.2% HR 1.19; 95% CI 0.71 to 1.98 p-value NR 4. Mean number of new or enlarging lesions on MRI per year	NA 4.1%/25 4.8%/21 NS NA	Any Adverse Event 1. 382 (82.2%) 2. 380 (82.3%) Early Discontinuation due to Adverse Event 1. 27 (5.8%) 2. 24 (5.2%) Serious Adverse Events 1. 48 (10.3%) 2. 38 (8.2%) 95% CI and p-values NR	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1 via IRT. Stratified by geographic region (Western Europe, Eastern Europe, North America & Australia, and Others) and by MS subtype (RRMS vs. SPMS). Baseline demographics were similar in both arms. Performance Bias: Low. Laboratory assessments that could lead to unblinding were not revealed to staff or sponsor study team. Matching oral and SC placebos were used to maintain treatment blinding. Detection Bias: Low. The investigators, the sponsor, and the steering committee were unaware of treatment assignment. MRI scans independently analyzed by staff blinded to treatment assignments. EDSS assessments completed by an independent clinician. Attrition Bias: High. More patients withdrew from the teriflunomide arm compared to ofatumumab. Reasons for study withdrawal were primarily due to patient decision. Reporting Bias: Low. Protocol available on-line. All prespecified outcomes reported. Other Bias: High. Sponsored by the manufacturer, Novartis. Data collected by investigators was analyzed by Novartis. The manuscript was drafted with medical writing assistance funded by the sponsor. Several investigators reported grant support from Novartis. **Applicability**: Patient: Patients were representative of MS population with EDSS scores ≤ 5.5, indicating patients were ambulatory and active. 40% of patients had not had previous DMD treatment and may have benefited from interferon or fumarate therapy. Intervention: Selected dose for ofatumumab in MS patients was proven to be the lowest, maximally effective dose in a Phase II trial.

		(Dimethyl fumarate: 1 month; Fingolimod: 2 months; Daclizumab: 4 months; Teriflunomide: 3.5 months; Rituximab, Ocrelizumab: 2 years) -PPMS -SPMS without disease activity -Disease duration > 10 years with EDSS score ≤ 2 -PML		1. 0.72 2. 4.0 Rate Ratio: 0.18 95% CI 0.15 to 0.22 P<0.001				Comparator: Teriflunomide, an IST with proven efficacy in reducing relapses, selected as an active comparator at recommended dosing. Outcomes: Annualized relapse rate used as primary outcome, similar to other DMD trials in MS. Setting: Both trials were conducted at 385 sites in 37 countries Europe, North America, South America, Australia, Asia, and Africa. 120 sites (31%) were located in the United States.
2. Hauser SL et al.[8] ASCLEPIOS II DB, AC, MC Phase 3 RCT	1. Ofatumumab 20 mg SC on days 0, 7, 14 and 28 followed by 20 mg SC every 4 weeks (plus teriflunomide-matching placebo capsule orally once daily) 2. Teriflunomide 14 mg orally once daily (plus ofatumumab-matching SC placebo injection) Duration: Variable based on when end of study criteria was met. Median Duration: 1.6 years Maximum duration: 30 months	Demographics: -Age: 38 y -Female: 67% -White: 87% -Median baseline EDSS score: 2.5 -No previous DMD treatment: 39% Key Inclusion Criteria: see ASCLEPIOS I Key Exclusion Criteria: see ASCLEPIOS I	ITT: 1. 481 2. 474 PP: 1. 398 2. 390 Attrition: 1.83 (17%) 2.84 (18%)	Primary Endpoint: Adjusted annualized relapse rate at median follow up of 1.6 years 1. 0.10 2. 0.25 Difference: -0.15; 95% CI -0.20 to -0.09; P<0.001 Secondary Endpoints: 1.Percentage of patients with worsening disability at 3 months (Kaplan-Meier estimate) 1. 10.5% 2. 14.6% HR 0.66; 95% CI 0.45 to 0.97 P-value NR 2. Percentage of patients with worsening disability at 6 months (Kaplan-Meier estimate) 1. 8.0% 2. 10.9% HR 0.76; 95% CI 0.49 to 1.17 p-value NR 3. Percentage of patients with disability	NA 4.1%/25 2.9%/35	Any Adverse Event 1. 409 (85%) 2. 408 (86.1%) Early Discontinuation due to Adverse Event 1. 27 (5.6%) 2. 25 (5.3%) Serious Adverse Event 1. 38 (7.9%) 2. 36 (7.6%) 95% CI and p-values NR	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: see ASCLEPIOS I Performance Bias: see ASCLEPIOS I Detection Bias: see ASCLEPIOS I Attrition Bias: Low. Attrition rates were similar in both groups. Reporting Bias: see ASCLEPIOS I Other Bias: see ASCLEPIOIS I **Applicability**: Patient: see ASCLEPIOS I Intervention: see ASCLEPIOS I Comparator: see ASCLEPIOS I Outcomes: see ASCLEPIOS I Setting: see ASCLEPIOS I

				improvement at 6 months (Kaplan-Meier estimate) 1. 12.3% 2. 8.1% HR 1.52; 95% CI 0.93 to 2.47 p-value NR 4. Mean number of new or enlarging lesions on MRI per year 1. 0.64 2. 4.15 RR 0.15; 95% CI 0.13 to 0.19; P<0.001	NS NA			

Abbreviations: AC = active comparator; ARR = absolute risk reduction; CI = confidence interval; DMD = disease-modifying drug; DB = double blind; EDSS = Expanded Disability Status Scale; Gd = gadolinium; HR = hazard ratio; IRT = Interactive Response Technology; IST = Immunosuppressive Therapy; ITT = intention to treat; MC = multi-center; MRI = magnetic resonance imaging; MS = multiple sclerosis; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; PP = per protocol; PML = progressive multifocal leukoencephalopathy; PPMS = primary progressive multiple sclerosis; RCT = randomized controlled trial; RR = rate ratio; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; SPMS = secondary progressive multiple sclerosis; y = years

NEW DRUG EVALUATION: Ponesimod

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.

Ponesimod is a selective, second-generation, $S1PR_1$ modulator. Other sphingosine 1-phosphate (S1P) receptor modulators include fingolimod, siponimod, and ozanimod. Ponesimod induces a rapid, dose-dependent, and reversible reduction of peripheral blood lymphocyte counts by blocking the egress of lymphocytes from lymphoid organs.[10] In contrast to fingolimod, which has a half-life of 6 to 9 days and slow elimination, ponesimod is eliminated within 1 week of discontinuation due to a half-life of 33 hours, and its pharmacologic effects can be rapidly reversed. Rapid elimination of ponesimod and the reversibility of its effects on lymphocyte levels allows the rapid return of normal immune system function, which may be beneficial in terms of safety for pregnancy planning, serious infections, or vaccinations.[10] Fingolimod, a first-generation, non-selective, S1P receptor modulator, can cause adverse events due to its pharmacologic effect on other S1P receptors expressed in diverse tissues, including cardiac myocytes. The specificity of ponesimod for subtype 1 of the S1P receptors is theorized to minimize undesirable effects related to interaction with other S1P receptor subtypes. Ponesimod received FDA approval March 2021 for treatment of relapsing forms of MS, including CIS, RRMS, and SPMS.[35] The FDA-approved dosing initiates ponesimod with a 14-day titration starting with 2 mg once daily and slowly increasing to the recommended maintenance dose of 20 mg orally once daily.[35] Ponesimod was evaluated in clinical trials as a treatment option for plaque psoriasis in adults, but has not been FDA-approved for this indication.

Clinical Efficacy:
Results from the Oral Ponesimod Versus Teriflunomide in Relapsing Multiple Sclerosis (OPTIMUM) trial contribute to the efficacy data for the use of ponesimod in relapsing MS, which are described and evaluated below in **Table 7.** The OPTIMUM trial was a multicenter, double-blind, active-comparator, phase 3 superiority RCT.[10] Patients with relapsing MS (n=1133) were randomized 1:1 to ponesimod 20 mg starting on day 15 or teriflunomide 14 mg once daily for 108 weeks. Ponesimod was slowly titrated upwards over 14 days, starting with 2 mg once daily to mitigate first-dose cardiac effects associated with S1P modulators. One hundred sixty two sites randomized patients across 28 countries in North America, Europe, Israel, and Turkey.[10] The primary endpoint was the annualized relapse rate based on the number of confirmed relapses per patient-year over 108 weeks. A relapse was defined as new, worsening or recurrent neurological symptoms that occurred at least 30 days after the onset of a preceding relapse, and that lasted at least 24 hours, in the absence of fever or infection.[10] The new, worsening or recurrent neurological symptoms were to be evaluated by the treating neurologist and, if all the elements of the above definition had been verified, and in the absence of another, better explanation of the patient's symptoms, the event was considered as a relapse.[10] A relapse was confirmed by the treating neurologist only when the patients' symptoms were accompanied by an increase in EDSS scores or functional system scores from a previous clinical assessment.[10] Secondary endpoints included changes in fatigue-related symptoms evaluated via the FSIQ–RMS score at week 108 and an assessment of 12-week and 24-week confirmed disability accumulation based on changes in the EDSS score. An increase of at least 1.5 with a baseline EDSS score of 0.0, at least 1.0 with baseline EDSS score of 1.0 to 5.0, or at least 0.5 with a baseline EDSS score of 5.5 or more was considered confirmed change.[10] Cumulative number of combined unique active lesions (CUALs) on MRI from baseline to week 108 (defined as new Gd+ T1 lesions plus new or enlarging T2 lesions) was an additional secondary endpoint.[10]

In total, there were 242 confirmed relapses reported for ponesimod compared with 344 for teriflunomide over the 108-week study period.[10] Ponesimod reduced annualized relapse rate by 30.5% at week 108 compared with teriflunomide (mean annualized relapse rate, 0.202 vs 0.290; rate ratio, 0.695; 99% CI, 0.536-0.902; P<0.001).[10] The change in FSIQ-RMS weekly symptom score from baseline to week 108 was lower (where higher scores indicate more fatigue) for fatigue symptoms in the ponesimod group than the teriflunomide group.[10] The least-square means were 0.01 (ponesimod) versus 3.56 (teriflunomide); mean difference, −3.57; 95% CI, −5.83 to −1.32; P=0.002.[10] The risk of 12-week confirmed disability accumulation was not statistically different between ponesimod and teriflunomide (10.1% vs. 12.4% respectively; HR, 0.83; 95% CI, 0.58-1.18; P=0.29).[10] Similar results were observed in exploratory disability accumulation over 24 weeks (8.1% vs 9.9%; HR, 0.84; 95% CI, 0.57 to 1.24; P=0.37).[10] For the secondary efficacy outcome of cumulative number of (CUALs) per year from baseline to week 108, ponesimod reduced the number of new inflammatory lesions on brain MRI scans by 56% compared to teriflunomide (1.405 vs.3.164; rate ratio, 0.44; 95% CI, 0.36 to 0.54; P<0.001).[10]

Trial Limitations:
Baseline EDSS scores (mean, 2.6) and the proportion of patients with EDSS scores of 3.5 or less (83.5%) are indicative of a relatively low level of disability, and few 12-week confirmed disability accumulation were observed in both the ponesimod and teriflunomide groups, leading to a limitation in the ability to detect significant differences between treatment groups.[10] The low rate of confirmed disability accumulation in both arms and the fact that teriflunomide demonstrated a significant benefit on 12-week confirmed disability progression in 2 separate trials in subjects with relapsing MS[36,37] suggests that OPTIMUM was underpowered to detect a difference within the 2-year treatment period.[10] Although the investigators limited the percentage of patients with SPMS to 15%, there were a very limited number of patients with SPMS (2.5%) enrolled in the trial. Finally, the patient reported outcome used to evaluate changes in fatigue related to relapsing MS was recently developed by the manufacturer of ponesimod. Although the FSIQ-RMS tool has been validated, it has only been used in clinical trials evaluating the efficacy of ponesimod.[24] A reduction of 6.3 points in the FSIQ-RMS symptom scale was considered a meaningful change threshold.[10]

The reported overall improvement for ponesimod compared to teriflunomide in FSIQ-RMS symptom score was 3.57 on a 100 point score, which raises some uncertainty regarding the clinical significance for improved fatigue symptoms.

Clinical Safety:
Overall, the proportion of patients who experienced at least 1 TEAE was similar between the 2 groups (ponesimod 88.8% vs. teriflunomide 88.2%).[10] The most common TEAEs (≥10% in either group) were an increased ALT level (19.5% vs. 9.4%), nasopharyngitis (19.3% vs. 16.8%), headache (11.5% vs. 12.7%), upper respiratory tract infection (10.6% vs. 10.4%), and alopecia (3.2% vs. 12.7%) in the ponesimod versus teriflunomide groups, respectively.[10] Two patients in the teriflunomide group died: 1 of coronary artery insufficiency and 1 of MS (adjudicated as sudden cardiac death).[10] Both deaths were considered by the investigators to be not associated with the study drug. Overall, TEAEs leading to treatment discontinuation were more frequent in the ponesimod group (8.7% vs. 6.0%]; dyspnea, an increased ALT level, an increased aspartate aminotransferase level, and macular edema were the most commonly reported reasons.[10] The overall incidence of first-dose heart rate and rhythm adverse effects on day 1 (at a 2 mg dose) of up-titration or treatment reinitiation was 2.1% in the ponesimod group (n = 12) compared with 0.4% (n = 2) in the teriflunomide group, with none reported as serious or leading to treatment discontinuation.[10] No second-degree or higher-degree atrioventricular blocks occurred.[10]

Table 5. Adverse Reactions Reported In The OPTIMUM Study Occurring In At Least 5% Of Ponesimod-Treated Patients And At A Higher Rate Than Teriflunomide-Treated Patients[35]

Adverse Reaction	Ponesimod (n=565)	Teriflunomide (n=566)
Upper respiratory infection	37%	34%
Hepatic transaminase elevation	23%	12%
Hypertension	10%	9%
Urinary trat infection	6%	5%
Dyspnea	5%	1%
Dizziness	5%	3%

Look-alike / Sound-alike Error Risk Potential: No other drugs identified

Comparative Endpoints:
Clinically Meaningful Endpoints:
1) Number of Relapses
2) Worsening Fatigue at 108 weeks
3) Disability Accumulation over 3 and 6 months
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Annualized Relapse Rate

Table 6. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Sphingosine 1-phosphate receptor 1 modulator – reduces peripheral blood lymphocyte counts by blocking the egress of lymphocytes from lymphoid organs
Oral Bioavailability	84% (10 mg dose)
Distribution and Protein Binding	Volume of Distribution: 160 Liters; Protein Binding: > 99%
Elimination	Renal: 10 to 18% unchanged: Hepatic: 57 to 80% (16% as unchanged drug); Total Body Clearance: 3.8 Liters/hour
Half-Life	33 hours
Metabolism	Extensively metabolized to inactive metabolites by hepatic enzymes

Table 7. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Kappos L, et al.[10] Phase 3 MC, DB, AC, RCT	1. Ponesimod 20 mg PO once daily 2. Teriflunomide 14 mg PO once daily	Demographics: 1. Mean age: 36.8 yo 2. Women: 64.9% 3. White: 97.4% 4. Mean baseline EDSS score: 2.6 5. RRMS: 97.5% SPMS: 2.5% 6.Disease modifying drugs received within 2 years prior to study enrollment: 39.5% Key Inclusion Criteria: 1.Adults aged 18 to 55 yo with RRMS or SPMS 2. 1 or more MS relapses 12 months prior to study enrollment or 2 or more MS relapses 24 months prior to enrollment 2. Ambulatory with an EDSS score ≤ 5.5 3. Subjects could be treatment-naïve or previously treated with interferon, glatiramer acetate, dimethyl fumarate or natalizumab. Key Exclusion Criteria:	ITT: 1. 567 2. 566 PP: 1. 471 2. 473 Attrition: 1.96 (16.9%) 2.93 (16.4%)	Primary Endpoint: Mean Annualized Relapse Rate 1. 0.202 2. 0.290 Rate Ratio: 0.695 99% CI, 0.536 to 0.902 P<0.001 Secondary Endpoints: A. Least squares mean FSIQ-RMS weekly symptoms score change 1. -0.01 2. 3.56 Mean Difference: -3.57 95% CI -5.83 to -1.32 P=0.002 B. Patients with confirmed 12-	NA NA NA NS	TEAEs: 1. 502 (88.8%) 2. 499 (88.2%) TEAEs leading to treatment discontinuation: 1. 49 (8.7%) 2. 34 (6.0%) Serious Adverse Events 1. 49 (8.7%) 2. 46 (8.1%) 95% CI and p-values NR Fatal TEAEs 1. 0 2. 2 (0.4%) 95% CI and p-values NR	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1 to ponesimod or teriflunomide via IRT. Patients were stratified by prior use of MS DMD (yes/no) and baseline EDSS (≤ 3.5 vs. >3.5). Baseline characteristics were similar between groups. Performance Bias: Low. Patients received ponesimod & matching placebo tablet OR teriflunomide & matching placebo capsule during the first 14 days of the study. First doses were observed by a first-dose administrator as potential adverse effects of ponesimod (effects on heart rate and AV conduction) could have resulted in unblinding. Access to information regarding adverse effects observed with the first dose was not permitted for all members of the study team. At day 15, subjects were switched to receiving 1 capsule containing either ponesimod or teriflunomide. Investigators, study staff, and subjects were all blinded to treatment arm. Detection Bias: Low. EDSS scores were assessed by independent evaluators. Treating neurologists evaluated symptoms indicative of relapse. Attrition Bias: Low. Attrition rates were similar between groups. However, there were fewer treatment discontinuations due to efficacy in the ponesimod arm compared to teriflunomide (1.9% vs. 4.3%) and more treatment discontinuations in the ponesimod arm due to adverse effects compared with teriflunomide (6.5% vs. 2.4%). Reporting Bias: Low. Protocol available on-line. All prespecified outcomes reported.

		1.Patient with contraindications to magnetic resonance imaging. 2.Treatment with beta-blockers, verapamil, digoxin or any other anti-arrhythmic or heart rate lowering medication within 15 days of randomization 3. Subjects with progressive forms of MS 4.Treatment with alemtuzumab, mitoxantrone, fingolimod, or other investigational S1P1 modulators 5. Treatment with systemic corticosteroids and ACTH within 30 days of randomization except for treatment of MS relapses. 6. Subjects with significant medical conditions or therapies for such conditions (e.g., cardiovascular, pulmonary, immunological, hepatic, ophthalmological, ocular) or lactating or pregnant women are not eligible to enter the study.		week disability accumulation 1. 57 (10.1) 2. 70 (12.4%) HR: 0.83 95% CI 0.58 to 1.18 P=0.29 C. Cumulative number of combined active lesions per year 1. 1.405 2. 3.164 Rate Ratio: 0.444 95% CI 0.36 to 0.54 P<0.001	NA			Other Bias: Unclear. Funding was provided by Janssen Research & Development LLC, and the OPTIMUM study was supported by Actelion Pharmaceuticals, part of Janssen Pharmaceutical Companies. Janssen employees were responsible for the design and conduct of the study and collection, management, analysis, and interpretation of the data. Several study investigators received substantial grant funding from Actelion or Janssen. **Applicability**: Patient: Patients enrolled in the study had relatively low levels of disability (mean baseline EDSS score: 2.6). Most of the patients had RRMS (97.5%). Only 2.5% of patients had SPMS. Most patients (62.5%) were naïve to MS disease modifying treatment. Intervention: Safety and efficacy of ponesimod 20 mg once daily dosing was evaluated in a Phase 2 trial. Comparator: Teriflunomide is an oral MS drug with proven efficacy in RRMS and SPMS. Fingolimod may have been a better active comparator, since it has a similar mechanism of action as ponesimod. Outcomes: Annualized relapse rate used as primary outcome, similar to other DMD trials in MS. Setting: 162 centers across 28 countries in North America, Europe, Mexico, Israel, and Turkey.

Abbreviations: AC = active comparator; ACTH = adrenocorticotropin hormone; ARR = absolute risk reduction; CI = confidence interval; DMD = disease-modifying drug; DB = double blind; EDSS = Expanded Disability Status Scale; Gd = gadolinium; HR = hazard ratio; IRT = Interactive Response Technology; IST = Immunosuppressive Therapy; ITT = intention to treat; MC = multi-center; MRI = magnetic resonance imaging; MS = multiple sclerosis; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; PP = per protocol; PML = progressive multifocal leukoencephalopathy; PPMS = primary progressive multiple sclerosis; RCT = randomized controlled trial; RR = rate ratio; RRMS = relapsing-remitting multiple sclerosis; SC = subcutaneous; SPMS = secondary progressive multiple sclerosis; TEAEs = treatment-emergent adverse events: y = years

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
glatiramer acetate	COPAXONE	SUB-Q	SYRINGE	Y
interferon beta-1a	AVONEX PEN	INTRAMUSC	PEN IJ KIT	Y
interferon beta-1a	AVONEX	INTRAMUSC	SYRINGEKIT	Y
interferon beta-1a/albumin	AVONEX	INTRAMUSC	KIT	Y
interferon beta-1a/albumin	REBIF REBIDOSE	SUB-Q	PEN INJCTR	Y
interferon beta-1a/albumin	REBIF	SUB-Q	SYRINGE	Y
interferon beta-1b	BETASERON	SUB-Q	KIT	Y
interferon beta-1b	EXTAVIA	SUB-Q	KIT	Y
alemtuzumab	LEMTRADA	INTRAVEN	VIAL	N
cladribine	MAVENCLAD	ORAL	TABLET	N
dalfampridine	AMPYRA	ORAL	TAB ER 12H	N
dalfampridine	DALFAMPRIDINE ER	ORAL	TAB ER 12H	N
dimethyl fumarate	DIMETHYL FUMARATE	ORAL	CAPSULE DR	N
dimethyl fumarate	TECFIDERA	ORAL	CAPSULE DR	N
diroximel fumarate	VUMERITY	ORAL	CAPSULE DR	N
fingolimod HCl	GILENYA	ORAL	CAPSULE	N
glatiramer acetate	COPAXONE	SUB-Q	SYRINGE	N
glatiramer acetate	GLATIRAMER ACETATE	SUB-Q	SYRINGE	N
glatiramer acetate	GLATOPA	SUB-Q	SYRINGE	N
interferon beta-1b	BETASERON	SUB-Q	VIAL	N
interferon beta-1b	EXTAVIA	SUB-Q	VIAL	N
monomethyl fumarate	BAFIERTAM	ORAL	CAPSULE DR	N
ocrelizumab	OCREVUS	INTRAVEN	VIAL	N
ofatumumab	KESIMPTA PEN	SUB-Q	PEN INJCTR	N
ozanimod hydrochloride	ZEPOSIA	ORAL	CAP DS PK	N
ozanimod hydrochloride	ZEPOSIA	ORAL	CAPSULE	N
peginterferon beta-1a	PLEGRIDY PEN	SUB-Q	PEN INJCTR	N
peginterferon beta-1a	PLEGRIDY	SUB-Q	SYRINGE	N
siponimod	MAYZENT	ORAL	TAB DS PK	N
siponimod	MAYZENT	ORAL	TABLET	N
teriflunomide	AUBAGIO	ORAL	TABLET	N
fingolimod HCl	GILENYA	ORAL	CAPSULE	
Ponesimod	PONVORY	ORAL	TABLET	

Appendix 2: Abstracts of Comparative Clinical Trials

Cheshmavar M, Mirmosayyeb O, Badihian N, Badihian S, Shaygannejad V.

Rituximab and glatiramer acetate in secondary progressive multiple sclerosis: randomized clinical trial. *Acta Neurologica Scandinavica.* 2021;143(2):178-187.[33]

BACKGROUND: Treatment options for secondary progressive multiple sclerosis (SPMS) are limitedly investigated. We aimed to compare the efficacy of rituximab (RTX) and glatiramer acetate (GA) in SPMS patients.

METHOD: This open, randomized clinical trial was conducted on 84 SPMS patients, assigned to receive RTX or GA for 12 months. In RTX group, patients received 1 g intravenous RTX primarily and then every 6-months. In GA group, patients received 40 mg of GA 3-times/week subcutaneously. We measured EDSS as the primary outcome and neuroimaging findings, relapse rate (RR), and side effects as the secondary outcomes.

RESULTS: Seventy-three patients completed the study (37 and 36 in RTX and GA groups, respectively). The mean EDSS increased from 3.05 +/- 1.01 to 4.14 +/- 0.91 in RTX group ($p < 0.001$) and from 3.22 +/- 1.20 to 4.60 +/- 0.67 in GA group ($p < 0.001$). No statistically significant difference was observed in EDSS between two groups ($F(1, 67) = 3.377$; $p = 0.071$). The number of active lesions in brain and cervical spine decreased with no difference between groups ($p > 0.05$). Also, RR decreased in both groups without significant difference between them ($F(1, 67) = 0.390$; $p = 0.534$). Non-serious complications were observed in both groups.

CONCLUSION: Neither RTX nor GA affects EDSS in SPMS patients. They are equally effective in the relapse control of these patients.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to February Week 3 2021, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to February 26, 2021

1 exp Glatiramer Acetate/	1359
2 exp Interferon-beta/	8808
3 alemtuzumab.mp.	2925
4 exp Fingolimod Hydrochloride/	2248
5 ocrelizumab.mp.	349
6 peginterferon beta.mp.	59
7 teriflunomide.mp.	453
8 exp cladribine	1241
9 Dimethyl Fumarate/or diroximel fumarate.mp or Fumarates	3241
10 dalfampridine.mp or 4-aminopyridine	2523
11 monomethyl fumarate.mp	72
12 ofatumumab.mp	532
13 ozanimod.mp or Sphingosine 1 Phosphate Receptor Modulators/	120
14 siponimod.mp	109
15 teriflunomide.mp	453
16 exp Multiple Sclerosis	44227
17 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	22333
18 17 and 16	5956
19 limit 18 to (humans and yr="2020 -Current" and (clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta-analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews))	49

Appendix 4: Prescribing Information Highlights

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

KESIMPTA® (ofatumumab) injection, for subcutaneous use
Initial U.S. Approval: 2009

----------INDICATIONS AND USAGE----------
KESIMPTA is a CD20-directed cytolytic antibody indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. (1)

----------DOSAGE AND ADMINISTRATION----------
- Hepatitis B virus (HBV) and quantitative serum immunoglobulins screening are required before the first dose. (2.1)
- Administer KESIMPTA by subcutaneous injection only. (2.2, 2.3)
- Initial Dosing: 20 mg administered at Week 0, 1, and 2. (2.2)
- Subsequent Dosing: 20 mg administered monthly starting at Week 4. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
- Injection: 20 mg/0.4 mL solution in a single-dose prefilled Sensoready® pen (3)
- Injection: 20 mg/0.4 mL solution in a single-dose prefilled syringe (3)

----------CONTRAINDICATIONS----------
- Active HBV infection. (4)

----------WARNINGS AND PRECAUTIONS----------
- Infections: Delay KESIMPTA administration in patients with an active infection until the infection is resolved. Vaccination with live-attenuated or live vaccines is not recommended during treatment with KESIMPTA and after discontinuation, until B-cell repletion. (5.1)
- Injection-Related Reactions: Management for injection-related reactions depends on the type and severity of the reaction. (5.2)
- Reduction in Immunoglobulins: Monitor the level of immunoglobulins at the beginning, during, and after discontinuation of treatment with KESIMPTA until B-cell repletion. Consider discontinuing KESIMPTA if a patient develops a serious opportunistic infection or recurrent infections if immunoglobulin levels indicate immune compromise. (5.3)
- Fetal Risk: May cause fetal harm based on animal data. Advise females of reproductive potential of the potential risk to a fetus and to use an effective method of contraception during treatment and for 6 months after stopping KESIMPTA. (5.4, 8.1)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence greater than 10%) are upper respiratory tract infection, headache, injection-related reactions, and local injection site reactions. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 8/2020

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

PONVORY™ (ponesimod) tablets, for oral use
Initial U.S. Approval: 2021

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

PONVORY is a sphingosine 1-phosphate receptor modulator indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. (1)

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

- Assessments are required prior to initiating PONVORY (2.1)
- Titration is required for treatment initiation (2.2)
- The recommended maintenance dosage is 20 mg taken orally once daily (2.2)
- First-dose monitoring is recommended for patients with sinus bradycardia, first- or second-degree [Mobitz type I] atrioventricular (AV) block, or a history of myocardial infarction or heart failure (2.3)

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

Tablets: 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, and 20 mg (3)

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

- In the last 6 months, experienced myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure requiring hospitalization, or Class III/IV heart failure (4)
- Presence of Mobitz type II second-degree, third-degree AV block, or sick sinus syndrome, unless patient has a functioning pacemaker (4)

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

- Infections: PONVORY may increase the risk of infections. Obtain a complete blood count (CBC) before initiating treatment. Monitor for infection during treatment and for 1-2 weeks after discontinuation. Do not start PONVORY in patients with active infection. (5.1)
- Bradyarrhythmia and Atrioventricular Conduction Delays: PONVORY may result in a transient decrease in heart rate; titration is required for treatment initiation. Check an electrocardiogram (ECG) to assess for preexisting cardiac conduction abnormalities before starting PONVORY. Consider cardiology consultation for conduction abnormalities or concomitant use with other drugs that decrease heart rate. (5.2, 7.2, 7.3)
- Respiratory Effects: May cause a decline in pulmonary function. Assess pulmonary function (e.g., spirometry) if clinically indicated. (5.3)
- Liver Injury: Discontinue if significant liver injury is confirmed. Obtain liver function tests before initiating PONVORY. (5.4)
- Increased Blood Pressure (BP): Monitor BP during treatment. (5.5)
- Cutaneous Malignancies: Periodic skin examination is recommended. (5.6)
- Fetal Risk: Women of childbearing potential should use effective contraception during and for 1 week after stopping PONVORY. (5.7)
- Macular Edema: An ophthalmic evaluation is recommended before starting treatment and if there is any change in vision while taking PONVORY. Diabetes mellitus and uveitis increase the risk. (5.8)

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

Most common adverse reactions (incidence at least 10%) are upper respiratory tract infection, hepatic transaminase elevation, and hypertension. (6.1).

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

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

- Vaccines: Avoid live *attenuated* vaccines during and for up to 1-2 weeks after treatment with PONVORY (7.4)
- Strong CYP3A4 and UGT1A1 Inducers: Coadministration with PONVORY is not recommended. (7.5)

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

Hepatic Impairment: PONVORY is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh class B and C). (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 03/2021

Ofatumumab (Kesimpta™)

Goal(s):

- Restrict drug use to patient populations in which the drug has been shown to be effective and safe.
- Ensure appropriate baseline monitoring to minimize patient harm.

Length of Authorization:

- 6 to 12 months

Requires PA:

- Kesimpta™ (ofatumumab) pharmacy or physician administered claims
- Requests for Arzerra™ should be reviewed under the Oncology PA.

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the medication FDA-approved or compendia-supported for the requested indication?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the drug being used to treat an OHP-funded condition?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #5
5. Is the patient an adult (age ≥18 years) diagnosed with relapsing multiple sclerosis?	**Yes:** Go to #6	**No:** Go to #7

Approval Criteria		
6. Has the patient failed trials for at least 2 drugs indicated for the treatment of relapsing multiple sclerosis?	**Yes:** Document drug and dates trialed: 1._____(dates) 2._____(dates) Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Has the patient been screened for an active Hepatitis B infection?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Is the drug prescribed by or in consultation with a neurologist?	**Yes**: Approve ofatumumab 20 mg SC at week 0, 1 and 2 followed by 20 mg once monthly starting at week 4.	**No:** 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?	**Yes:** Approve for 12 months. Document baseline assessment and physician attestation received.	**No:** Pass to RPh; Deny; medical appropriateness.

P&T/DUR Review: *6/21 (DM)*
Implementation: *TBD*

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
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have a diagnosis of Multiple Sclerosis?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Go to #4	**No:** 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)?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #5
5. Does the patient have a history of seizures?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #6
6. Does the patient have moderate or severe renal impairment (est. GFR <50 mL/min)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #7

Approval Criteria		
7. Is the patient ambulatory with a walking disability requiring use of a walking aid **OR;** have moderate ambulatory dysfunction and does not require a walking aid AND able to complete the baseline timed 25-foot walk test between 8 and 45 seconds?	**Yes:** Approve initial fill for 2-month trial.	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has the patient been taking dalfampridine for ≥2 months with documented improvement in walking speed while on dalfampridine (≥20% improvement in timed 25-foot walk test)?	**Yes:** Go to #2	**No:** Pass to RPh. Deny; medical appropriateness
2. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Approve for 12 months	**No:** 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: *6/21(DM); 8/20 (DM); 6/20; 11/17; 5/16; 3/12*
Implementation: *8/16, 9/1/13*

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:
- All oral MS therapy including:
  - Sphingosine 1-phosphate receptor modulators (e.g. fingolimod, ozanimod, ponesimod, siponimod, etc.)
  - Teriflunomide
  - Fumarate salts (e.g., dimethyl fumarate, monomethyl fumarate, diroximel fumarate, etc.)
  - Cladribine

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for an FDA-approved form of multiple sclerosis in the appropriate age range? (see Table 1)	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics Committee and do not require PA.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #4
4. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Go to #5	**No:** 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, ofatumumab, ocrelizumab, or mitoxantrone)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #6
6. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #7
7. Is there documentation of recommended baseline testing to mitigate safety concerns (Table 2)?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness.
8. Is the prescription for teriflunomide?	**Yes:** Go to #9	**No:** Go to #11
9. Is the patient of childbearing potential?	**Yes:** Go to #10	**No:** Approve for up to 6 months.
10. Is there documentation of a negative pregnancy test as well as reliable contraception OR documentation that provider has assessed pregnancy risk and discussed pregnancy avoidance with the patient?~~that the patient is currently on a reliable form of contraception?~~	**Yes:** Approve for up to 6 months.	**No:** Pass to RPh. Deny; medical appropriateness.
11. Is the prescription for a sphingosine 1-phosphate receptor modulator (Table 1)?	**Yes:** Go to #12	**No:** Go to #15

Approval Criteria		
12. Does the patient have evidence of macular edema?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #13
13. Does the patient have preexisting cardiac disease, risk factors for bradycardia, or is on an anti-arrhythmic, beta-blocker, or calcium channel blocker?	**Yes:** Go to #14	**No:** Approve up to 6 months.
14. Has the patient had a cardiology consultation before initiation (see clinical notes)?	**Yes:** Approve up to 6 months.	**No:** Pass to RPh. Deny; medical appropriateness.
15. Is the prescription for a fumarate product?	**Yes:** Go to # 16	**No:** Go to #17
16. Does patient have a baseline CBC with lymphocyte count greater than 500/µL?	**Yes:** Approve for up to 6 months.	**No:** Pass to RPh. Deny; medical appropriateness.
17. Is the request for cladribine?	**Yes:** Go to #18	**No:** Approve for up to 6 months
18. Is the patient of reproductive potential?	**Yes:** Go to # 19	**No:** Go to # 20
19. Is there documentation of a negative pregnancy test as well as reliable contraception OR documentation that provider has assessed pregnancy risk and discussed pregnancy avoidance with the patient? ~~(or female partner of a male patient) is on a reliable form of contraception?~~	**Yes:** Go to # 20	**No:** Pass to RPh. Deny; medical appropriateness
20. Has the patient had an inadequate response to or they are unable to tolerate alternative MS treatment?	**Yes:** Approve for 6 months	**No:** 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?	**Yes:** Approve for 12 months. Document baseline assessment and physician attestation received.	**No:** Pass to RPh; Deny; medical appropriateness.

Table 1. Dosing And FDA-Approved Indications for Oral MS Drugs

Generic Name	FDA Indication (Adults unless otherwise indicated)		
	CIS	**RRMS**	**SPMS**
Cladribine		X	X
Fingolimod	X *(≥ 10 years)*	X *(≥ 10 years)*	X *(≥ 10 years)*
Siponimod	X	X	X
Ozanimod	X	X	X
Ponesimod	X	X	X
Teriflunomide	X	X	X
Dimethyl Fumarate	X	X	X
Monomethyl Fumarate	X	X	X
Diroximel Fumarate	X	X	X
Abbreviations: CIS = clinically isolated syndrome; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis			

Table 2. FDA-recommended Baseline Safety Assessments (see clinical notes for details)

	Negative Pregnancy Test	LFTs	CBC with lymphocyte count	Ophthalmic Exam	Varicella Zoster Antibodies	CYP2C9 genotype	Other Screening
Fumarate salts		X	X (>500)				
Fingolimod*	X	X	X	X	X		
Ozanimod*	X	X	X	X	X		
Ponesimod	X	X	X	X	X		

Siponimod*	X	X	X	X	X	X	
Teriflunomide	X (box warning)	X (box warning)	X				
Cladribine	X (box warning)	X	X (WNL)		X		TB; HBV; HIV; HCV; MRI for PML
Abbreviations: HBV = hepatitis B; HCV = hepatitis C; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging; PML = progressive multifocal leukoencephalopathy; TB = tuberculosis; WNL = within normal limits							

* sphingosine 1-phosphate receptor modulators

Sphingosine 1-Phosphate Receptor Modulators (fingolimod, ozanimod, ponesimod, siponimod) Clinical Notes:

- Because of bradycardia and atrioventricular conduction, patients must be observed for 4 to 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, ozanimod or siponimod with caution. A cardiology evaluation should be performed before considering treatment.
- An ophthalmology evaluation should be repeated 3-4 months after fingolimod, ozanimod, ponesimod, or siponimod initiation with subsequent evaluations based on clinical symptoms.
- Patients starting on siponimod therapy must be tested for CYP2C9 variants to determine CYP2C9 genotype before starting siponimod. Siponimod is contraindicated in patients with a CYP2C9*3/*3 genotype. The recommended maintenance dosage in patients with a CYP2C9*1/*3 or *2/*3 genotype is 1 mg. The recommended maintenance dosage in all other patients is 2 mg.

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 upper 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.

Fumarate Salts (Dimethyl Fumarate, Monomethyl Fumarate, Diroximel Fumarate) Clinical Notes:

- Fumarate salts 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 x10^3 cells/mm^3 (equivalent to <0.8 cells/µL). A transient increase in mean eosinophil counts was seen during the first 2 months of therapy.
- Fumarate salts should be held if the WBC falls below 2 x10^3 cells/mm^3 or the lymphocyte count is below 0.5 x10^3 cells/mm^3 (cells/µL) and permanently discontinued if the WBC did not increase to over 2 x10^3 cells/mm^3 or lymphocyte count increased to over 0.5 x10^3 cells/mm^3 after 4 weeks of withholding therapy.
- Patients should have a CBC with differential monitored every 6 to 12 months.

Cladribine Clinical Notes:
- Cladribine is not recommended for use in patients with clinically isolated syndrome (CIS) because of its safety profile.
- Prior to initiating cladribine follow standard cancer screening guidelines because of the risk of malignancies.
- Obtain a CBC with differential including lymphocyte count. Lymphocytes must be: within normal limits before initiating the first treatment course and at least 800 cells per microliter before initiating the second treatment course. If necessary, delay the second treatment course for up to 6 months to allow for recovery of lymphocytes to at least 800 cells per microliter. If this recovery takes more than 6 months, the patient should not receive further treatment with cladribine.
- Infection screening: exclude HIV infection, perform TB and hepatitis screening. Evaluate for active infection; consider a delay in cladribine treatment until any acute infection is fully controlled.
- Administer all immunizations according to immunization guidelines prior to starting cladribine. Administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting cladribine.
- Obtain a baseline (within 3 months) magnetic resonance imaging prior to the first treatment course because of the risk of progressive multifocal leukoencephalopathy (PML).

P&T/DUR Review: *6/21 (DM); 8/20 (DM); 6/20; 11/17; 11/16; 9/15; 9/13; 5/13; 3/12*
Implementation: *9/1/20; 1/1/18; 1/1/17; 1/1/14; 6/21/2012*

Ocrelizumab (Ocrevus™)

Goal(s):

- Restrict use of ocrelizumab in patients with relapsing-remitting multiple sclerosis (RRMS) to those who have failed multiple drugs for the treatment of RRMS.
- Ensure appropriate baseline monitoring to minimize patient harm.

Length of Authorization:

- 6 to 12 months

Requires PA:

- Ocrevus™ (ocrelizumab) pharmacy or physician administered claims

Covered Alternatives:

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

Approval Criteria		
9. What diagnosis is being treated?	Record ICD10 code.	
10. Is the medication FDA-approved or compendia-supported for the requested indication?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
11. Is the drug being used to treat an OHP-funded condition?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
12. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #5
13. Is the patient an adult (age ≥18 years) diagnosed with relapsing multiple sclerosis?	**Yes:** Go to #6	**No:** Go to #7

Approval Criteria		
14. Has the patient failed trials for at least 2 drugs indicated for the treatment of relapsing multiple sclerosis?	**Yes:** Document drug and dates trialed: 1._____(dates) 2._____(dates) Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
15. Has the patient been screened for an active Hepatitis B infection?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
16. Is the drug prescribed by or in consultation with a neurologist who regularly treats multiple sclerosis?	**Yes**: Approve ocrelizumab 300 mg every 2 weeks x 2 doses followed by 600mg IV every 6 months for 12 months	**No:** 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.	**Yes:** Approve for 12 months. Document baseline assessment and physician attestation received.	**No:** Pass to RPh; Deny; medical appropriateness.

P&T/DUR Review: *6/21(DM); 6/20; 11/17 (DM); 1/17*
Implementation: *7/1/20; 1/1/18; 4/1/17*

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:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for an FDA-approved form of multiple sclerosis?	**Yes:** Go to #3.	**No:** Pass to RPH; Deny for medical appropriateness.
3. Will the prescriber consider a change to a Preferred MS product?	**Yes:** Inform provider of covered alternatives in the class.	**No:** Go to #4.
4. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Go to #5.	**No:** Pass to RPH; Deny for medical appropriateness.
5. Does the patient have any of the following: • Adherence issues necessitating less frequent administration • Dexterity issues limiting ability to administer subcutaneous injections	**Yes:** Approve for up to one year.	**No:** Pass to RPH; Deny for medical appropriateness.

Natalizumab (Tysabri®)

Goal(s):

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

Length of Authorization:

- Up to 12 months

Requires PA:

- Natalizumab (Tysabri®)

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Has the patient been screened for John Cunningham (JC) Virus?	**Yes:** Go to #3	**No:** Pass to RPH; Deny for medical appropriateness
3. Does the patient have a diagnosis of relapsing multiple sclerosis (CIS, RRMS, or SPMS)?	**Yes:** Go to #4	**No:** Go to #6
4. Has the patient failed trials for at least 2 drugs indicated for the treatment of RRMS?	**Yes:** Document drug and dates trialed: 1._____(dates) 2._____(dates) Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
5. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Approve for 12 months	**No:** Pass to RPH; Deny for medical appropriateness.
6. Does the patient have Crohn's Disease?	**Yes:** Go to #7	No: Pass to RPH; Deny for medical appropriateness.
7. Has the patient been screened for latent or active tuberculosis and if positive, started tuberculosis treatment?	**Yes:** Go to #8	**No:** Pass to RPH; Deny for medical appropriateness**.**
8. Has the patient failed to respond to at least one of the following conventional immunosuppressive therapies for ≥6 months: • Mercaptopurine, azathioprine, or budesonide; or • Have a documented intolerance or contraindication to conventional therapy? • AND • Has the patient tried and failed a 3 month trial of Humira?	**Yes:** Approve for up to 12 months. Document each therapy with dates. If applicable, document intolerance or contraindication(s).	**No:** Pass to RPh. Deny; medical appropriateness.

P&T / DUR Action: *6/21(DM); 10/20 (DM); 11/17*
Implementation: *1/1/18*

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Drug Class Update with New Drug Evaluation: Heart Failure Therapy Focused Update of Sacubitril/Valsartan

Date of Review: June 2021

Date of Last Review: May 2017
Dates of Literature Search: 03/01/2017 – 01/31/2021
Brand Name (Manufacturer): Verquvo® (Merck)
Dossier Received: yes

Generic Name: Vericiguat

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

Purpose for Class Update:
To review new evidence for efficacy and harms of sacubitril/valsartan in the treatment of chronic heart failure (HF), including evidence supporting its expanded indication for all patients with chronic heart failure, across the spectrum of ejection fraction (EF). This review will also evaluate the evidence and place in therapy of vericiguat in the treatment of heart failure with reduced ejection fraction (HFrEF).

Research Questions:
1. What is the evidence for sacubitril/valsartan to reduce mortality and cardiovascular (CV) morbidities when used to manage chronic heart failure with heart failure with preserved ejection fraction (HFpEF)?
2. Are there subgroups of patients in which sacubitril/valsartan may be safer or more effective when used to manage chronic HFpEF?
3. What is the evidence for vericiguat to reduce mortality and CV morbidities when used to manage chronic HFrEF?
4. What are the safety and harms of vericiguat; and if available, how do these compare to the safety and harms of ACE-inhibitors (ACE-Is) and angiotensin II receptor blockers (ARBs) when used to manage chronic HFrEF?
5. Are there subgroups of patients in which vericiguat may be safer or more effective when used to manage chronic HFrEF?

Conclusions:
- There is insufficient evidence that sacubitril/valsartan reduces CV outcomes in patients with HFpEF. There was no significant difference in the composite of CV death or total heart failure (HF) hospitalizations in a phase 3, double-blind, active comparator, randomized controlled trial in adults with symptomatic HF and a left ventricular ejection fraction ≥ 45%.[1] The effect of sacubitril/valsartan on the primary endpoint was driven primarily by the total HF hospitalizations component.
- Subgroup analyses of this trial for the primary efficacy endpoint showed that subjects with a left ventricular ejection fraction (LVEF) below the median (LVEF 57%) appeared to be more beneficial (rate ratio [RR] 0.78, 95% CI 0.64-0.95) than with an LVEF above the median (RR 1.00, 95% CI 0.81-1.23). [1] The FDA labeling notes that benefits are most clearly evident in patients with LVEF below normal. Additionally, sacubitril/valsartan seemed to reduce the risk of HF hospitalization in women more than men.

Author: Megan Herink, PharmD

- There is insufficient evidence that sacubitril/valsartan reduces CV outcomes or improves quality of life in pediatric patients with HFrEF. There is low quality evidence based on a 12-week interim analysis of a 52-week RCT that sacubitril/valsartan results in a mean percent reduction in N-terminal -proB natriuretic peptide (NT-proBNP) of 44%, similar to the reduction seen in adults in clinical trials, but was not statistically superior to the reduction seen with enalapril. [2]
- There is moderate quality evidence that vericiguat reduces CV death or HF hospitalization compared to placebo (35.5% vs. 38.5%; Hazard Ratio [HR] 0.90; 95% CI 0.82 to 0.98; Number Needed to Treat [NNT] 34) in patients with symptomatic advanced HFrEF on goal directed medical therapy with a recent decompensation and elevated NT-proBNP but does not reduce all-cause mortality. [3]
- There is low quality evidence of no significant difference in discontinuations due to adverse events between vericiguat and placebo, but a higher rate of hypotension and anemia. [3] Vericiguat is contraindicated in pregnancy and should not be used with long-acting nitrates or phosphodiesterase type 5 (PDE5) inhibitors due to its effects on the nitric oxide pathway. An unknown safety concern includes its higher rate of CV death and hospitalization among subjects with the highest baseline NT-proBNP levels in the clinical study.[3]

Recommendations:
- Rename the "ACEIs, ARBs and DRIs" PDL class to "Inhibitors of the Renin-Angiotensin-Aldosterone System (RAAS)" and include sacubitril/valsartan as a non-preferred agent in the class.
- Update prior authorization criteria for sacubitril/valsartan to include expanded FDA indications (**Appendix 6**).
- Maintain vericiguat as non-preferred and require prior authorization (**Appendix 6**) to ensure appropriate use in patients on goal directed therapy with advanced symptomatic HFrEF.

Summary of Prior Reviews and Current Policy
- There is low to moderate quality evidence that sacubitril/valsartan 97/103 mg twice daily (BID) can reduce risk of death from CV causes or hospitalization for HFrEF by an absolute difference of 4.7% compared to enalapril 10 mg BID (21.8% vs. 26.5%, respectively; Hazard Ratio [HR]=0.80 (95% Confidence Interval [CI] 0.73-0.87; p<0.001; number needed-to-treat [NNT] 22).[4]
- There is low quality evidence, based on a secondary endpoint, that sacubitril/valsartan may reduce all-cause mortality, driven almost entirely by reduction in CV mortality, by an absolute difference of 2.8% compared to enalapril (17.0% vs. 19.8%, respectively; HR=0.84 (95% CI, 0.76-0.93; p<0.001; NNT 36).[4]
- There is insufficient evidence to determine if the results seen were driven by the maximum daily dose of valsartan (320 mg) or by the addition of the neprilysin inhibitor sacubitril to maximally dosed valsartan. Additional studies will help guide place in therapy for sacubitril/valsartan in the management of HFrEF, including whether a neprilysin inhibitor with an ARB will replace an ACE-I or ARB in most HFrEF patients
- Current prior authorization limits use of sacubitril/valsartan to patients with HFrEF with ejection fraction <40%, on maximally tolerated ACE-I or ARB and a recommended beta-blocker.

Background:
Heart failure (HF) is a clinical syndrome caused by a structural and/or functional cardiac abnormality, resulting in reduced cardiac output and/or elevated cardiac pressures. It results in symptoms such as edema, shortness of breath and fatigue and is often recognized by signs of elevated jugular venous pressure, pulmonary crackles, and pulmonary edema. Heart failure is further classified into HFrEF (left ventricular ejection fraction ≤ 40%) and HFpEF (left ventricular ejection fraction > 50%). [5] A left ventricular ejection between 41% and 49% is referred as heart failure with mid-range ejection fraction (HFmrEF). The goals of management of HFrEF are to prevent hospital admission and improve survival, and to relieve signs (e.g., edema) and symptoms (e.g., dyspnea). The cornerstone of drug therapy in chronic HFrEF is inhibition of the neurohormonal activation present in HFrEF that promotes cardiac remodeling.[5,6] The most well-studied

system is the renin-angiotensin-aldosterone system (RAAS), and inhibition of RAAS has been shown to have a significant impact on the pathophysiology and progression of HF.[5,6] Drugs that inhibit neurohormonal activation in HFrEF have consistently proven to reduce all-cause mortality in chronic HFrEF patients (NYHA class I-IV).[7] These drugs include an ACE-I (alternatively, an ARB if an ACE-I is not tolerated), a cardioselective beta-blocker (bisoprolol, carvedilol, or sustained-release metoprolol succinate), and for most patients, a mineralocorticoid (aldosterone) receptor antagonist (spironolactone or eplerenone).

An ACE-I can reduce mortality and hospitalizations, improve symptoms, exercise tolerance and performance, and improve quality of life in patients with HFrEF.[6,7] The benefits of ACE inhibition are seen in patients with mild, moderate or severe symptoms of HF and in patients with or without coronary artery disease (CAD).[7] The addition of a beta-blocker to an ACE-I further improves morbidity outcomes and mortality in these patients.[6] Long-term treatment with the aforementioned beta-blockers also improve symptoms of HF, improve functional status, and enhance the patient's overall sense of well-being.[6,7] However, these benefits should not be considered a class effect. Other beta-blockers, including metoprolol tartrate, were less effective in HF trials.[7] Nebivolol demonstrated a modest but non-significant reduction in the primary endpoint of all-cause mortality or CV hospitalization but did not affect mortality alone in an elderly population with both reduced and preserved EF.[8] Aldosterone antagonists are recommended to reduce morbidity and mortality in patients with NYHA class III-IV who have reduced EF (≤35%), though their benefits probably extend to all patients with HFrEF.[6,7] Patients with NYHA class II with reduced EF also benefit from an aldosterone antagonist if they have a history of previous CV hospitalization or have elevated plasma natriuretic peptide levels.[7] However, renal function and potassium should be routinely monitored because of risk for hyperkalemia in susceptible patients, such as those with renal insufficiency.

In most controlled clinical trials designed to evaluate mortality, the dose of the ACE-I/ARB, beta-blocker and aldosterone antagonist was not determined by the patient's therapeutic response but was increased until the predetermined target dose was reached. Current guidelines recommend clinicians use every effort to reach the study doses achieved in clinical trials that have demonstrated efficacy to reduce CV events (see **Table 1**).[6,7]

Table 1. Drugs Shown to Improve Mortality/Morbidity in Chronic Heart Failure with Reduced Ejection Fraction. Adapted from 2012 ESC Guidelines.[6]

ACE Inhibitors	Angiotensin-2 Receptor Blockers	Beta-Blockers	Aldosterone Antagonists
• Captopril 50 mg TID* • Enalapril 10-20 mg BID • Lisinopril 20-40 mg QDay^ • Ramipril 5 mg BID • Trandolapril 4 mg QDay*	• Candesartan 32 mg QDay • Losartan 150 mg QDay^ • Valsartan 160 mg BID	• Bisoprolol 10 mg QDay • Carvedilol 25-50 mg BID • Metoprolol succinate (XL/ER) 200 mg QDay	• Eplerenone 50 mg QDay • Spironolactone 25-50 mg QDay

Abbreviations: BID = twice daily; QDay = once daily; TID = three times daily; XL/ER = extended-release formulation
* Indicates an ACE inhibitor where the dosing target is derived from post-myocardial infarction trials.
^ Indicates drugs where a higher dose has been shown to reduce morbidity/mortality compared with a lower dose, but there is no substantive placebo-controlled RCT and the optimum dose is uncertain.

Ventricular diastolic dysfunction is the main characteristic in HFpEF, likely caused by hypertensive left ventricular remodeling.[8] Atrial fibrillation occurs commonly with HFpEF, and up to 30% of patients may have normal levels of natriuretic peptides. Patients with HFpEF tender to be older and more commonly women compared to HFrEF. Unlike in HFrEF, no therapy has been shown to improve outcomes in patients with HFpEF. Current treatment strategies including symptomatic management of volume overload and controlling coexisting conditions such as hypertension and atrial fibrillation.[8] Therapy with ACE-I/ARBs and beta-blockers are limited for use in HFpEF to those who have alternative indications. Spironolactone has been shown to reduce the rate of heart failure hospitalizations but had no significant effect on all-cause mortality or hospitalizations from any cause.[8]

Neprilysin is a neutral endopeptidase that degrades vasoactive peptides such as natriuretic peptides and bradykinin.[9] Natriuretic peptides, which include atrial natriuretic peptide and B-type natriuretic peptide (BNP), are secreted by the heart in response to increased cardiac wall stress (and also secreted by other organs in response to other stimuli).[9] Inhibition of neprilysin increases the levels of these peptides and counteracts the neurohormonal activation associated with vasoconstriction, sodium retention and cardiac remodeling. However, the combined use of an ACE-I and a neprilysin inhibitor (enalapril/omapatrilat) was associated with serious angioedema when studied in HF. Subsequently, sacubitril, a prodrug converted into the neprilysin inhibitor sacubitrilat, was studied in combination with an ARB (valsartan) in patients with HFrEF in the PARADIGM-HF trial.[4] Sacubitril/valsartan is a first-in-class angiotensin receptor neprilysin inhibitor (ARNI). The PARADIGM-HF trial provided moderate quality evidence that sacubitril/valsartan can reduce risk of death from CV causes or hospitalization for HF by an absolute difference of 4.7% compared to enalapril 10 mg BID [21.8% vs. 26.5%, respectively; HR=0.80 (95% CI 0.73 to 0.87; p<0.001; NNT 22)].[4] Additionally, sacubitril/valsartan was associated with more episodes of symptomatic hypotension than enalapril (14.0% vs. 9.2%, respectively), but a lower incidence of cough and hyperkalemia.[4] In February 2021, the FDA label for sacubitril/valsartan was expanded and includes "to reduce the risk of CV death and HF hospitalization in adults patients with chronic HF (including HFpEF)".[10] Current HF guidelines recommend use of sacubitril/valsartan for patients with HFrEF who remain symptomatic despite optimal medical therapy with an ACE-I or ARB, and beta-blocker.[11] The pivotal trials required run-in periods demonstrating tolerance to ACE-I or ARB therapy prior to initiation of sacubitril/valsartan.

In addition to sacubitril/valsartan, additional therapies have been evaluated in chronic heart failure, including sodium-glucose cotransporter-2 (SGLT2) inhibitors and vericiguat (**Tables 2 and 3**). Vericiguat is a soluble guanylate cyclase (sGC) stimulator, causing vasodilation through the nitric oxide pathway.

Table 2: Characteristics of Cardiovascular Outcome trials for Newer Therapies for chronic Heart Failure[1,3,4,12,13]

	PARADIGM-HF	PARAGON-HF	EMPEROR-Reduced	DAPA-HF	VICTORIA
Study Drug	Sacubitril/Valsartan	Sacubitril/Valsartan	Empagliflozin	Dapagliflozin	Vericiguat
Patient Population	HFrEF (EF ≤ 35%)	HFpEF (EF ≥ 45%)	HFrEF (EF ≤ 40%)	HFrEF (EF ≤ 40%)	HFrEF (EF ≤ 45%) with worsening HF
Comparator	Enalapril	Valsartan	Placebo	Placebo	Placebo
Mean LVEF	29%	58%	27%	31%	29%
NYHA III-IV	25%	19%	25%	33%	41%
Median Follow-up	27 months	35 months	16 months	18 months	11 months

Abbreviations: EF: ejection fraction; HF: heart failure, HFrEF: heart failure with reduced ejection fraction, HFpEF: heart failure with preserved ejection fraction, LVEF: left ventricular ejection fraction; NYHA: New York Heart Association class

Table 3: Summary of Results from Cardiovascular Outcome Trials in HFrEF[1,3,4,12,13]

Outcome	Sacubitril/Valsartan ARR/NNT	Empagliflozin ARR/NNT	Dapagliflozin ARR/NNT	Vericiguat ARR/NNT
CV death and heart failure hospitalization*	4.7% / 22	5.3% / 19	4.9% / 21	3%/ 34
Death from any cause	2.8% / 36	NS	2.3% / 44	NS
CV Death	3.2% / 32	NS	1.9% / 53	NS

Abbreviations: ARR: absolute risk reduction; CV: cardiovascular; NNT: number needed to treat; NS: not significant
*analyzed as time to first event

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, 3 systematic reviews[14-16] were excluded due to poor quality[14-16] (e.g, indirect network-meta analyses), wrong study design of included trials (e.g., observational)[17], comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical)[18]. One systematic review from the Cochrane Collaboration evaluating the efficacy of beta-blockers and inhibitors of the RAAS for HFpEF was identified.[19] However, at the time there were no completed studies available with sacubitril/valsartan in HFpEF.

New Guidelines:
Three guidelines were excluded due to poor quality rigor of development and systematic approach.[7,20,21] Two of these are consensus statements.[7,20]

American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Failure Society of America (HFSA): Focused Update of the 2013 Guideline on the Management of Heart Failure[11]

The 2017 focused update of the 2013 guideline included revisions on biomarkers, new therapies for HFrEF, updates on HFpEF and new data on important comorbidities. Part 1 of this guideline included an update on new pharmacological therapy, including sacubitril/valsartan in HFrEF, and was reviewed in a previous class update. There were no major changes to recommendations regarding therapy with an ARNI in this update. There remains a Class I recommendation based on level B-R evidence that in patients with chronic symptomatic HFrEF who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality. An ARNI should not be administered concomitantly with ACE-I or within 36 hours of the last dose due to the risk of angioedema.

National Institute for Health and Care Excellence (NICE): Chronic heart failure in adults: diagnosis and management.[22]

The NICE updated its guidelines for chronic heart failure in adults in 2018. Recommendations were based on systematic reviews of best available evidence and consideration of cost effectiveness. The guideline recommendations were intended for primary care clinicians. The guidelines recommend first-line therapy with an ACE-I and beta blocker for those patients with HFrEF. The following are key guideline statements regarding therapy with sacubitril/valsartan:

- Sacubitril/valsartan is recommended as an option for treatment symptomatic chronic HFrEF, only in people:
    - With NYHA class II to IV symptoms, and
    - Left ventricular ejection fraction of 35% or less, and

- Who are already taking a stable dose of an ACE-I or ARB
- Treatment with sacubitril/valsartan should be started by a heart failure specialist with access to a multidisciplinary heart failure team

New Formulations or Indications:

- In October 2019, the FDA labeling for sacubitril/valsartan was expanded to include pediatric patients age 1 year and older with heart failure and systemic left ventricular systolic dysfunction.[2] This expanded approval was based on a 12-week analysis of the 52-week PANORAMA-HF study. The PANORAMA-HF trial was a two-part, multi-center, randomized, double-blind, parallel group, 52-week study.[23] This trial remains unpublished and cannot fully be assessed for quality and risk of bias. Key inclusion criteria included children aged 1-17 years with chronic heart failure due to left ventricular systolic dysfunction (LVEF ≤40%) previously on an ACE or ARB. Key exclusion criteria included patients with a single ventricle or systemic right ventricle, patients listed for heart transplant, with sustained or symptomatic dysrhythmias, with restrictive or hypertrophic cardiomyopathy, active myocarditis, history of angioedema, moderate-to-severe obstructive pulmonary disease, and serum potassium >5.3 mmol/L. Phase one was a pharmacokinetic study to that demonstrated similar exposure in pediatric patients with studied doses (3.1 mg/kg) as adults on 97/103 mg of sacubitril/valsartan.

  Phase 2 of the study evaluated the efficacy and safety of sacubitril/valsartan (target dose 3.1 mg/kg BID) compared to enalapril (target dose 0.2 mg/kg BID) in pediatric HF patients. The primary efficacy outcome was originally designed using a Global Rank endpoint including death, listing for heart transplant, worsening of heart failure and quality of life. However, due to challenges with recruitment, the NT-proBNP was used as a bridging biomarker to evaluate clinical efficacy. The interim analysis for primary efficacy was designed to demonstrate a 30% or greater reduction in NT-proBNP from baseline at week 12 for sacubitril/valsartan compared to enalapril.

  At week 12, sacubitril/valsartan (n=54) resulted in a 15.6% greater reduction than enalapril (n=54) (adjusted geometric mean ratio 0.84; 95% CI 0.67-1.06) for the mean ratio of NT-proBNP to baseline levels but did not reach superiority over enalapril. FDA analysis noted that the mean percent reduction at week 12 (44%) was similar to reduction seen in adults in the PARADIGM-HF trial. [2] There was less of a treatment response seen in the subgroup of patients age 1 to < 6 years old. Results at 52 weeks are not available.

- In February 2021, sacubitril/valsartan was FDA approved for all patients with chronic HF, including those with HFpEF.[10] This expanded approval was based on the results of the PARAGON-HF trial.

  The PARAGON-HF trial **(Table 4)** was a multi-center, randomized, double-blind active comparator trial in 43 countries.[1] The trial evaluated the efficacy of sacubitril/valsartan in patients with symptomatic heart failure and an ejection fraction of 45% or higher, including both those with mildly reduced and normal LVEF. The primary endpoint was the composite of total heart failure hospitalizations and death from CV causes. Total number of hospitalizations was used instead of the more common time-to-first event analysis since patients with HFpEF have a higher rate of hospitalizations and lower rate of CV death compared to patients with HFrEF. The trial contained a pre-randomization run-in period of an average of 14 days of valsartan, followed by an average of 19 days of sacubitril/valsartan to assess for tolerability. After the run-in, patients were randomized to a target dose of valsartan 160 mg twice daily or a target dose of sacubitril-valsartan 97/103 mg twice daily. Only individuals who tolerated sacubitril/valsartan 49/51 mg twice daily were eligible for randomization. Overall, there was no significant difference in the primary outcome of total HF hospitalizations and CV death with 12.8 events per 100 patient-yr in the sacubitril/valsartan group and 14.6 per 100 patient-year in the valsartan group (RR 0.87; 95% CI 0.75 to 1.01). This endpoint was primarily driven by the rate of HF hospitalizations. Based on the power calculation, the difference in events between groups was smaller than anticipated.

While the primary endpoint was found to be non-significant, the FDA determined that the primary endpoint was primarily driven by the reduction in heart failure hospitalizations, whereas the CV death endpoint approached neutrality.[24] The FDA was intrigued by the subgroup analysis which determined those with moderately reduced ejection fraction below the median (≤ 57%) appeared to receive benefit from sacubitril/valsartan more than those with a higher ejection fraction with a rate ratio of 0.78 (95% CI 0.64 to 0.95), which is consistent with the PARADIGM trial results.[1,24] The applicant (Novartis) determined a possible cause for non-significant results in PARAGON could be due to rejection of primary events during adjudication due to an effort to maximize specificity for the primary efficacy endpoint. They also reported that more flexibility in clinical judgement would have reversed some of the diagnoses. The clinical events committee used strict criteria for adjudicating hospitalizations for heart failure, which may have reduced event counts due to insufficient documentation. The FDA review of the new indication asked the applicant to re-evaluate events which were possibly rejected as a primary endpoint event and determine a probability that these endpoints which, while marked negative for the trial, may have been positive events. After re-analysis of events from investigator rather than clinical events committee, the primary endpoint was found to have a rate ratio of 0.84 (95% CI 0.74 to 0.97, p=0.014).[24] The pre-specified exploratory expanded composite endpoint adding urgent care visits (RR 0.86; 95% CI 0.75-0.99; p=0.04) and re-adjudication analysis of unconfirmed HF hospitalizations (RR 0.86; 95% CI 0.75-1.00; p=0.04) contributed to the FDA decision along with evidence from the PARADIGM-HF study.[24]

The trial was funded by Novartis and found to have a low risk of bias. The pre-randomization run in periods increase the risk of unblinding and exclude high risk individuals who may experience adverse events. A total of 5746 participants entered the valsartan phase with 541 discontinuations (9.4%), and 5205 participants entered the sacubitril/valsartan phase with 384 discontinuations (7.3%).[1] Generalizability and applicability of study results remains limited based on no difference between the treatment group and placebo. Since patients with HFpEF have lower circulating neprilysin levels, a neprilysin inhibitor may be less effective. While the investigators did report a change in quality of life, as measured by the Kansas City Cardiomyopathy questionnaire (KCCQ) score, this score has a minimal clinically important difference (MCID) of 5 points[25], which was not seen in the study. Subgroup analysis suggests a possible benefit in patients with LVEF less than or equal to 57% (RR 0.78, 95% CI 0.64-0.95) compared to those with higher baseline LVEF (RR 1.00, 95% CI 0.81-1.23). The FDA reviewers note that benefits are clearly more evident in patients with LVEF below normal and clinical judgement should be used in deciding who to treat. There was also a more pronounced benefit seen in women (RR 0.73; 95% CI 0.59-0.90) compared to men (RR 1.03; 95% CI 0.85- 1.25). Slightly over half (52%) of participants were female. Reasons for this difference are not entirely clear but could be due to several considerations. The normal LVEF range is higher in women than in men; however, women have more evidence of contractile dysfunction for a given EF.[26] Since sacubitril/valsartan is more effective in patients with left ventricular systolic dysfunction, women may benefit more. Other differences that may contribute to a difference is more pronounced age-related arterial stiffening in women and sex differences in natriuretic peptide biology.[26]

Table 4: Evidence table for sacubitril/valsartan in heart failure with HFpEF

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints N (%) RR,HR (95% CI)	ARR/NNT	Safety Outcomes N (%) P value	ARI/NNH	Quality Rating Risk of Bias/Applicability
Paragon-HF[1] MC, R, AC, DB	1. Sacubitril/Valsartan 97/103 BID (ARNI) 2. Valsartan 160 BID (ARB) Study Phases -ARB run-in (15 days IQR 12-22 days) -ARNI run-in (19 days IQR 15-23 days) -1:1 Randomization to either ARNI or ARB	Demographics: Age: 72 years Females: 51% White: 81% Asian:12.5% Black: 2% NYHA Class I: 3% NYHA Class II: 77% NYHA Class III: 19% NYHA Class IV: 0% LVEF: 57.5% ±8% Ischemic cause: 36% BB: 79.5% Diuretic: 95% ACE/ARB: 86% MCRA: 26% Key Inclusion Criteria: Age>= 50 NYHA class II to IV LVEF >= 45% Evidence of structural HD On diuretic therapy Key Exclusion Criteria: Any prior LVEF < 40% SBP < 110 Acute decompensated HF eGFR < 30 K+ > 5.2 ACS Coronary or carotid artery disease likely require surgery Life expectancy < 3 years	ITT ARNI: 2407 ARB: 2389 Attrition ARNI: 370 (15.4%) ARB: 387 (16.2%)	Primary Endpoint: HF Hospitalizations and CV death: ARNI: 894 (37.1%) ARB: 1009 (42.2%) RR 0.87 (0.75 to 1.01) Secondary Endpoints: Death from any cause ARNI: 342 (14.2%) ARB: 349 (14.6%) HR 0.97; 95% CI 0.84-1.13 Change in KCCQ score MCID for KCCQ: 5 points ARNI: -1.6 points +/- 0.4 ARB: -2.6 points +/-0.4 RD 1.0 (Range: 0.0-2.1) Renal composite outcome* ARNI: 33 (1.4%) ARB: 64 (2.7%) HR 0.50; 95% CI 0.33-0.77 *death from renal failure, end-stage renal disease, or decrease in eGFR >50% from baseline	NS NS NA 1.3% / NNT 77	Discontinuations due to AE: ARNI: 370 (15.4%) ARB: 387 (16.2%) *p-value not reported Hypotension ARNI: 380 (15.8%) ARB: 257 (10.8%) p<0.001 Angioedema ARNI: 14 (0.6%) ARB: 4 (0.2%) P=0.02	NA ARI 5%/ NNH 20 ARI 0.4%/ NNH 250	**Risk of Bias** (low/high/unclear): Selection bias: Low; blinding with computer generated sequence using interactive response technology, baseline characteristics similar. Performance bias: unclear; blinding of participants and investigators, double dummy design. However, run-in period increases the risk of unblinding. Detection bias: low; outcome assessors and data analysts blinded Attrition bias: Low; <1% dropout in both groups, however dropout occurred prior to randomization (9.4% dropout, n=541, in valsartan run-in phase, 7.4% dropout, n=384, in ARNI run-in phase.) Publication bias: Low; study protocol available, prespecified outcomes of interest reported **Applicability**: Patient: Run-in period excluded higher risk patients and those at higher risk for adverse events. Since patients with HFpEF have lower circulating neprilysin levels, a neprilysin inhibitor may be less effective. Lacked racial diversity. Intervention: maintenance dose of ARNI designed to yield systemic exposure of valsartan equivalent to 320 mg/day. 82% in ARNI group achieved target dose vs. 85% in ARB group. Comparator: valsartan may have potential beneficial effect in HFpEF and impacted lower than expected treatment difference. Outcomes: clinically relevant outcomes with composite endpoint driven more by decreased morbidity. Used total hospitalizations, including recurrent, instead of more common time to first-event analysis.

								Setting: Multicenter study with 12% in North America.

Abbreviations [alphabetical order]: AC = Active control; ACS = Acute coronary syndrome; AE = adverse events; ARB = Angiotensin receptor blocker; ARI = absolute risk increase; ARNI: Angiotensin receptor neprolysin inhibitor; ARR = absolute risk reduction; BB = beta blocker; BID = Twice per day; CI = confidence interval; CV = Cardiovascular; DB = Double Blind; eGFR = estimated glomerular filtration rate; HD = Heart Disease; HF = Heart Failure; HR = hazard ratio; IQR = Interquartile range; ITT = intention to treat; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; MC = Multi-Center; MCID = Minimum Clinically Important difference; MCRA = Mineralocorticoid Receptor antagonist; MD = mean difference; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NYHA = New York Heart Association; OR = Odds Ratio; PP = per protocol; R = Randomized; RD = Risk Difference; RR = relative risk; SAE = serious adverse events; SBP = Systolic Blood Pressure; SCr = Serum Creatinine;

Randomized Controlled Trials:

A total of 9 citations were manually reviewed from the initial literature search. After further review, 8 citations were excluded because of wrong study design[27-30] (e.g., post-hoc analysis, observational), comparator[31] (e.g., no control or placebo-controlled), study population[32] (e.g. acute MI) or outcome studied[33-35] (e.g., non-clinical). The trial supporting the new indication is included in the previous evidence table (**Table 4)** and the remaining trial is summarized in the table below (**Table 5**). Full abstracts are included in **Appendix 2**.

Table 5. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	
McMurry et al.[26] Prespecified subgroup analysis of PARAGON-HF trial	Sacubitril/valsartan (ARNI) 97/103 mg BID vs. valsartan (ARB) 160 mg BID	HFrEF (LVEF > 45%), structural heart disease, and elevated NP level	Composite of first and recurrent hospitalizations for heart failure and death from CV cause	Women ARNI: 391 (32%) ARB: 532 (43%) RR 0.73; 95% CI 0.60-0.90	Men ARNI: 503 (43%) ARB: 477 (41%) RR 1.02; 95% CI 0.83-1.24

Abbreviations: ARB: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; BID: twice daily; CI = confidence interval; CV: cardiovascular; HFrEF: heart failure with reduced ejection fraction; LVEF: left ventricular ejection fraction; NP: natriuretic peptide; RR: rate ratio

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.

Vericiguat is a soluble guanylate cyclase (sGC) stimulator, indicated to reduce the risk of CV death and HF hospitalization following a hospitalization for heart failure or need for outpatient intravenous (IV) diuretics, in adults with symptomatic chronic HF and ejection fraction less than 45%.[36] Soluble guanylate cyclase

stimulates production of cyclic guanosine monophosphate (cGMP), a signaling molecule involved in vascular smooth muscle relaxation, cardiac contractility, and cardiac remodeling. It is proposed that vericiguat works through the nitric oxide pathway to increase intracellular cGMP, thus improving myocardial and vascular function via vasodilation and reduction of cardiac afterload. Through a different pathway than sacubitril/valsartan, it also augments natriuretic peptides.

Vericiguat demonstrated no benefit in reducing the level of N-terminal pro-B natriuretic peptide (NT-pro BNP) in an earlier phase 2 study in stable HF.[37] Therefore, this study was designed to include patients with advanced symptomatic heart failure who had recently been hospitalized or received IV diuretics (recent decompensated) with higher baseline NT-pro BNP levels.

Clinical Efficacy:

Approval was based on one placebo-controlled, multi-center, double-blind RCT (VICTORIA) comparing vericiguat to placebo in adults with HFrEF (ejection fraction <45%), NYHA Class II-IV, and an elevated natriuretic peptide level following a worsening HF event (**Table 7**).[3] A worsening HF event was defined as HF hospitalization within the previous 6 months or use of IV diuretics within 3 months before randomization. This was a higher risk population with 41% of patients with NYHA Class III or IV and a baseline NT-proBNP of 2816 pg/ml. Most participants had a HF hospitalization within the last 3 months (67%). The median follow-up period was 10.8 months. Sixty percent of patients were on background therapy with a beta-blocker, mineralocorticoid antagonist, and a renin-angiotensin system inhibitor (ACE-I, ARB, or ARNI). Additionally, 93% of patients were on a beta-blocker, 73% were on an ACE-I or ARB, and 70% were on a mineralocorticoid antagonist. Patients in the vericiguat group were started on 2.5 mg once daily and titrated up to a target dose of 10 mg once daily. Dose modification were based on systolic blood pressure and symptomatic hypotension. After 12 months, 89.2% in the vericiguat group were receiving the 10 mg target dose.[37]

The primary outcome was first occurrence of the composite of CV death or HF hospitalization. There was a statistically significant reduction in the primary outcome at a median of 10.8 months with vericiguat compared to placebo (35.5% vs. 38.5%; HR 0.90; 95% CI 0.82 to 0.98; NNT 34) that was driven by HF hospitalizations. There was a non-significant reduction in death from CV causes and no significant difference in all-cause mortality (**Table 7**).

There did not appear to be differences in subgroups of gender, race, or geographic region. However, pre-specified subgroup analysis did not show a benefit in the subjects in the highest quartile of NT-proBNP at baseline (> 5314 pg/mL), but instead showed a higher rate of CV death in the vericiguat group compared to placebo (208 [34%] vs. 169 [29%]), driven by sudden cardiac death.[37] There was also no significant benefit in the primary outcome in the subgroup of participants age 75 or older (HR 1.04; 95% CI 0.88 – 1.21). Post hoc analysis identified a significant interaction for the outcome of CV death by the presence (HR 0.69; 95% CI 0.55-0.88) or absence. (HR 1.06; 95% CI 0.90-1.25) of an implantable cardioverter defibrillator (ICD) at baseline, suggesting that devices are protective.[37] The unfavorable trend in CV death was most notable among those in the highest baseline NT-proBNP quartile without a device at baseline (HR 1.38; 95% CI 1.08-1.75).[37] Based on these findings, the FDA did a focused search and concluded that vericiguat is not proarrhythmic but included the observations in the labeling.

Risk of bias was generally low in the study. There was a high rate of overall discontinuation in both groups, but an intention-to-treat analysis was used to evaluate the primary outcome. Generalizability and applicability to clinical practice is low based on the narrow patient population and many exclusion criteria. Sites in the United States contributed 8% of subject enrollment. With challenges in adherence with complex medication regimens and increasing costs, emphasis should be put on optimizing goal directed medications, including beta-blockers and inhibitors of the renin-angiotensin system. Only 15% of subjects were on sacubitril/valsartan and it is remains unknown if the combination would be synergistic or would increase adverse events including hypotension and syncope.

Vericiguat should not be used in patients with HFpEF, as a 6-month placebo-controlled study resulted in a higher rate of CV death with vericiguat compared to placebo (3.8% vs. 1.5%) and no improvement in the physical limitation score of the KCCQ.[37,38]

Clinical Safety:
Serious adverse events occurred in 32.8% of the patients in the vericiguat group and in 34.8% of the patients in the placebo group. The most common side effects that occurred more commonly with vericiguat than placebo included hypotension (16% vs. 15%) and anemia (10% vs. 7%).[36] Symptomatic hypotension occurred in 9.1% of the patients in the vericiguat group and in 7.9% of the patients in the placebo group (P=0.12), and syncope occurred in 4.0% of patients in the vericiguat group and in 3.5% of patients in the placebo group (P=0.30). Symptomatic hypotension and syncope are side effects of concern due to the vasodilatory mechanism of action of vericiguat. The FDA reviewers noted that they were not associated with serious events such as increased falls or fractures and anemia did not result in clinical bleeding.[24] Vericiguat may cause fetal harm and is contraindicated in pregnancy. Inclusion criteria included male or female confirmed to be postmenopausal, without childbearing potential or use of acceptable contraception.

Comparative Endpoints:

Clinically Relevant Endpoints:
1) Mortality (all-cause; secondary to cardiovascular causes)
2) Hospitalizations (secondary to cardiovascular causes)
3) Symptomatic relief (dyspnea on exertion, nocturnal dyspnea)
4) Quality of life

Primary Study Endpoint:
1) Composite (death from cardiovascular causes or first hospitalization from heart failure)

Table 6. Pharmacology and Pharmacokinetic Properties.[36]

Parameter	
Mechanism of Action	Vericiguat is a stimulator of soluble guanylate cyclase (sGC), an important enzyme in the nitric oxide (NO) signaling pathway. This catalyzes the synthesis of intracellular cyclic guanosine monophosphate (cGMP), a second messenger that plays a role in the regulation of vascular tone, cardiac contractility, and cardiac remodeling.
Oral Bioavailability	93%
Distribution and Protein Binding	44L; protein binding is about 98%
Elimination	Approximately 53% of the dose was excreted in urine (primarily as inactive metabolite) and 45% in feces (primarily as unchanged drug)
Half-Life	30 hours
Metabolism	Primarily undergoes glucuronidation by UGT1A9 and to a lesser extent, by UGT1A1 to form an inactive N-glucuronide metabolite. CYP-mediated metabolism is a minor clearance pathway (<5%).

Table 7. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints N (%) RR,RD (95% CI)	ARR/NNT	Safety Outcomes N (%) P value	ARR/NNH	Quality Rating Risk of Bias/Applicability
Victoria[3] MC, PC, DB, RCT	1. Vericiguat 10 mg daily 2. Placebo On background guideline-based medical therapy X 12 months	Demographics: Age: 67 years Females: 23.9% White: 64% Mean LVEF 29% NYHA II: 59% NYHA III: 40% NYHA IV:1.3% Key Inclusion Criteria: o Age>= 18 o NYHA class II to IV o HF hospitalization within 6 months or IV diuretic within 3 months o Elevated BNP or NT-proBNP o LVEF < 45% Key Exclusion Criteria: o SBP < 110 o Use of LA nitrates, NO donors and PDE5 inhibitors o ACS within 60 days o eGFR < 15 ml/min o Severe hepatic insufficiency o Current alcohol or drug abuse	ITT 1. 2526 2. 2524 Attrition 1. 610 (24%) 2. 565 (22%)	Primary Endpoint: HF Hospitalizations and CV death: 1. 897 (35.5%) 2. 972 (38.5%) HR 0.90; 95% CI 0.82-0.98 P=0.02 Death from CV cause 1. 414 (16.4%) 2. 441 (17.5%) HR 0.93; 95% CI 0.81-1.06 Death from any cause 1. 512 (20.3%) 2. 534 (21.2%) HR 0.95; 95% CI 0.84-1.07	ARR 3%/ NNT 34 NS NS	Discontinuations due to AE: 1. 177 (7%) 2. 159 (6.3%) Symptomatic Hypotension 1. 229 (9.1%) 2. 198 (7.9%) P=0.12	NA NS	**Risk of Bias** (low/high/unclear): Selection bias: low; treatment allocation and randomization using an interactive voice response system, baseline characteristics well balanced between groups. Performance bias: low; double blinded using double dummy approach Detection bias: low; Members of an independent clinical-events committee who were unaware of the trial-group assignments adjudicated all deaths and hospitalizations Attrition bias: unclear; high overall attrition but similar in each group and ITT analysis done for the primary outcome. Data on patients who withdrew were censored at the last available follow-up time. Publication bias: low; study protocol available, prespecified outcomes of interest reported **Applicability**: Patient: Narrow inclusion and exclusion criteria limits generalizability to patients with advanced symptomatic heart failure on guideline directed therapy. Intervention: Unclear if strong dose response based on Phase 2 data Comparator: placebo appropriate comparator based on potential place in therapy Outcomes: clinically relevant outcomes with composite endpoint driven more by decreased hospitalizations Setting: 694 sites in 42 countries. 11% from North America (8% from US), 14% Latin America, 23% Asia, 17% western Europe, 33.5% eastern Europe

Abbreviations [alphabetical order]: ACS = Acute coronary syndrome; AE = adverse event; ARR = absolute risk reduction; BID = Twice per day; BNP = brain natriuretic peptide; CI = confidence interval; CV = Cardiovascular; DB = Double-Blind; GFR = glomerular filtration rate; HD = Heart Disease; HF = Heart Failure; HR = hazard ratio; ITT = intention to treat; KCCQ = Kansas City Cardiomyopathy Questionnaire; LA = long acting; LVEF = left ventricular ejection fraction; MC = Multi-Center; MD = mean difference; N = number of subjects; NA = not applicable; NO = nitric oxide; NNH = number needed to harm; NNT = number needed to treat; NT-proBNP = N-terminal pro BNP; NYHA = New York Heart Association; OR = Odds Ratio; PC = placebo controlled; PDE5 inhibitor = phosphodiesterase 5 inhibitor; PP = per protocol; RCT = Randomized; RD = Risk Difference; RR = relative risk; SAE = serious adverse events; SBP = Systolic Blood Pressure

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Appendix 1: Current Preferred Drug List

ACEIs, ARBs, DRIs, and Sacubatril/Valsartan

Generic	Brand	Route	Form	PDL
benazepril HCl	BENAZEPRIL HCL	ORAL	TABLET	Y
benazepril HCl	LOTENSIN	ORAL	TABLET	Y
enalapril maleate	ENALAPRIL MALEATE	ORAL	TABLET	Y
enalapril maleate	VASOTEC	ORAL	TABLET	Y
irbesartan	AVAPRO	ORAL	TABLET	Y
irbesartan	IRBESARTAN	ORAL	TABLET	Y
lisinopril	LISINOPRIL	ORAL	TABLET	Y
lisinopril	PRINIVIL	ORAL	TABLET	Y
lisinopril	ZESTRIL	ORAL	TABLET	Y
losartan potassium	COZAAR	ORAL	TABLET	Y
losartan potassium	LOSARTAN POTASSIUM	ORAL	TABLET	Y
olmesartan	BENICAR	ORAL	TABLET	Y
olmesartan	OLMESARTAN MEDOXOMIL	ORAL	TABLET	Y
ramipril	ALTACE	ORAL	CAPSULE	Y
ramipril	RAMIPRIL	ORAL	CAPSULE	Y
telmisartan	MICARDIS	ORAL	TABLET	Y
telmisartan	TELMISARTAN	ORAL	TABLET	Y
valsartan	DIOVAN	ORAL	TABLET	Y
valsartan	VALSARTAN	ORAL	TABLET	Y
aliskiren	ALISKIREN	ORAL	TABLET	N
aliskiren	TEKTURNA	ORAL	TABLET	N
azilsartan medoxomil	EDARBI	ORAL	TABLET	N
candesartan cilexetil	ATACAND	ORAL	TABLET	N
candesartan cilexetil	CANDESARTAN CILEXETIL	ORAL	TABLET	N
captopril	CAPTOPRIL	ORAL	TABLET	N
enalapril maleate	EPANED	ORAL	SOLUTION	N
eprosartan mesylate	TEVETEN	ORAL	TABLET	N
fosinopril sodium	FOSINOPRIL SODIUM	ORAL	TABLET	N
lisinopril	QBRELIS	ORAL	SOLUTION	N
moexipril HCl	MOEXIPRIL HCL	ORAL	TABLET	N
perindopril erbumine	PERINDOPRIL ERBUMINE	ORAL	TABLET	N

quinapril HCl	ACCUPRIL	ORAL	TABLET	N
quinapril HCl	QUINAPRIL HCL	ORAL	TABLET	N
trandolapril	TRANDOLAPRIL	ORAL	TABLET	N
sacubitril/valsartan	ENTRESTO	ORAL	TABLET	

Unassigned in Preferred Drug List (STC class 72 – Vasodilators: Coronary)

Generic	Brand	Route	Form	PDL
vericiguat	VERQUVO	PO	TABLET	

Appendix 2: Abstracts of Comparative Clinical Trials

- John J V McMurray, Alice M Jackson, Carolyn S P Lam, Margaret M Redfield, et al. Effects of Sacubitril-Valsartan Versus Valsartan in Women Compared With Men With Heart Failure and Preserved Ejection Fraction: Insights From PARAGON-HF. *Circulation.* 2020 Feb 4;141(5):338-351. Epub 2019 Nov 17.

  Background: Unlike heart failure with reduced ejection fraction, there is no approved treatment for heart failure with preserved ejection fraction, the predominant phenotype in women. Therefore, there is a greater heart failure therapeutic deficit in women compared with men.

  Methods: In a prespecified subgroup analysis, we examined outcomes according to sex in the PARAGON-HF trial (Prospective Comparison of ARNI With ARB Global Outcomes in Heart Failure With Preserved Ejection Fraction), which compared sacubitril-valsartan and valsartan in patients with heart failure with preserved ejection fraction. The primary outcome was a composite of first and recurrent hospitalizations for heart failure and death from cardiovascular causes. We also report secondary efficacy and safety outcomes.

  Results: Overall, 2479 women (51.7%) and 2317 men (48.3%) were randomized. Women were older and had more obesity, less coronary disease, and lower estimated glomerular filtration rate and NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels than men. For the primary outcome, the rate ratio for sacubitril-valsartan versus valsartan was 0.73 (95% CI, 0.59-0.90) in women and 1.03 (95% CI, 0.84-1.25) in men (P interaction = 0.017). The benefit from sacubitril-valsartan was attributable to reduction in heart failure hospitalization. The improvement in New York Heart Association class and renal function with sacubitril-valsartan was similar in women and men, whereas the improvement in Kansas City Cardiomyopathy Questionnaire clinical summary score was less in women than in men. The difference in adverse events between sacubitril-valsartan and valsartan was similar in women and men.

  Conclusions: As compared with valsartan, sacubitril-valsartan seemed to reduce the risk of heart failure hospitalization more in women than in men. Whereas the possible sex-related modification of the effect of treatment has several potential explanations, the present study does not provide a definite mechanistic basis for this finding.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) ALL <1946 to April 09, 2021>

1	entresto.mp.	78
2	sacubitril.mp.	1159
3	Valsartan/	2363
4	heart failure.mp. or Heart Failure/	218026
5	cardiovascular outcomes.mp.	8844
6	Mortality/de [Drug Effects]	2
7	cardiovascular mortality.mp.	14354
8	Myocardial Infarction/ or major adverse cardiovascular events.mp. or Coronary Artery Disease/	229672
9	hospitalization.mp. or Hospitalization/	216868
10	quality of life.mp. or "Quality of Life"/	369617
11	2 and 3	202
12	1 or 11	272
13	5 or 6 or 7 or 8 or 9 or 10	814172
14	4 and 12	212
15	13 and 14	54
16	limit 15 to (yr="2017 -Current" and english and (clinical trial, phase iii or clinical trial, phase iv or comparative study or meta analysis or randomized controlled trial or "systematic review"))	12

Appendix 4: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

VERQUVO™ (vericiguat) tablets, for oral use
Initial U.S. Approval: 2021

WARNING: EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning.

- **Do not administer VERQUVO to a pregnant female because it may cause fetal harm. (4, 5.1, 8.1)**
- **Females of reproductive potential: Exclude pregnancy before the start of treatment. To prevent pregnancy, females of reproductive potential must use effective forms of contraception during treatment and for one month after stopping treatment. (2.2, 5.1, 8.3)**

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

VERQUVO is a soluble guanylate cyclase (sGC) stimulator, indicated to reduce the risk of cardiovascular death and heart failure (HF) hospitalization following a hospitalization for heart failure or need for outpatient IV diuretics, in adults with symptomatic chronic HF and ejection fraction less than 45%. (1)

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

- The recommended starting dose of VERQUVO is 2.5 mg orally once daily with food. (2.1)
- Double the dose of VERQUVO approximately every 2 weeks to reach the target maintenance dose of 10 mg once daily, as tolerated by the patient. (2.1)
- Tablets may be crushed and mixed with water for patients who have difficulty swallowing. (2.1)

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

Tablets: 2.5 mg, 5 mg and 10 mg (3)

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

- Patients with concomitant use of other soluble guanylate cyclase (sGC) stimulators. (4, 7.1)
- Pregnancy (4)

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

Most common adverse reactions reported in ≥5% are hypotension and anemia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- PDE-5 Inhibitors: Concomitant use is not recommended. (7.2)

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

- Lactation: Breastfeeding is not recommended (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 01/2021

Appendix 5: Key Inclusion Criteria

Population	**Chronic heart failure**
Intervention	Sacubitril/valsartan or vericiguat
Comparator	ACE inhibitor or angiotensin aldosterone receptor antagonist or placebo
Outcomes	Heart failure hospitalization, cardiovascular mortality, all-cause mortality, symptomatic improvement, quality of life
Timing	N/A
Setting	Inpatient hospital or outpatient clinic

Sacubitril/Valsartan (Entresto™)

Goal(s):

- Restrict use of sacubitril/valsartan in populations and at doses in which the drug has demonstrated efficacy.
- Encourage use of beta-blockers with demonstrated evidence of mortality reduction in heart failure with reduced ejection fraction.

Length of Authorization:

- 60 days to 12 months

Requires PA:

Sacubitril/valsartan (Entresto™)

Covered Alternatives:

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

Approval Criteria		
1. Is this a request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to Renewal Criteria	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code. Go to #3	
3. Does the patient have chronic heart failure (New York Heart Association [NYHA] Class II-IV)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the patient 17 years of age or younger?	**Yes:** Go to #5	**No:** Go to # 7
5. Does the patient have left ventricular systolic dysfunction (ejection fraction less than 40% (LVEF ≤ 40%)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the medication prescribed by or in consultation by a cardiologist or heart failure provider?	**Yes:** Approve for 3 months	**No:** Pass to RPh. Deny, medical appropriateness

Approval Criteria		
7. Has the patient tolerated a minimum daily dose an ACE-inhibitor or ARB listed in Table 1 for at least 30 days? *Note: ACE inhibitors must be discontinued at least 36 hours prior to initiation of sacubitril/valsartan*	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Does the patient have heart failure with reduced ejection fraction less than 40% (LVEF ≤ 40%)?	**Yes:** Go to #9	**No:** Approve for 3 months *Note: Benefits of therapy are most clearly evident in patients with left ventricular ejection fraction below normal. Use judiciously with higher baseline ejection fraction*
9. Is the patient currently on a maximally tolerated dose of carvedilol, sustained-release metoprolol succinate, or bisoprolol; and if not, is there a documented intolerance or contraindication to each of these beta-blockers? *Note: the above listed beta-blockers have evidence for mortality reduction in chronic heart failure at target doses and are recommended by heart failure guidelines.[1,2] Carvedilol and metoprolol succinate are preferred agents on the PDL.*	**Yes:** Approve for 3 months	**No:** Pass to RPh. Deny, medical appropriateness

Renewal Criteria		
1. Is the patient 18 years or older or at least 50 kg?	**Yes:** Go to #2	**No:** Go to #3
2. Is the patient currently taking sacubitril/valsartan at the target dose of 97/103 mg 2-times daily to a maximum dose as tolerated by the patient?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh and go to #4

Renewal Criteria		
3. Is the patient currently taking sacubitril/valsartan at the target dose in Table 2 or to a maximum dose as tolerated by the patient?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh and go to #4
4. What is the clinical reason the drug has not been titrated to the target dose?	Document rationale and approve for up to 90 days. Prior authorization required every 90 days until target dose achieved.	

Table 1. Minimum Daily Doses of ACE-inhibitors or ARBs Required.[1,2]

ACE-inhibitor		Angiotensin-2 Receptor Blocker (ARB)	
Captopril	100 mg/day	Candesartan	16 mg/day
Enalapril	10 mg/day	Losartan	50 mg/day
Lisinopril	10 mg/day	Valsartan	160 mg/day
Ramipril	5 mg/day	Olmesartan	10 mg/day
Trandolapril	2 mg/day	Irbesartan	150 mg/day
Fosinopril	20 mg/day		

Abbreviations: BID = twice daily; QDay = once daily; mg = milligrams; TID = three times daily.

Notes:
- Patients must achieve a minimum daily dose of one of the drugs listed for at least 30 days to improve chances of tolerability to the target maintenance dose of sacubitril/valsartan 97/103 mg 2-times daily.[3]
- Valsartan formulated in sacubitril valsartan 97/103 mg 2-times daily is bioequivalent to valsartan 160 mg 2-times daily.[4]
- It is advised that patients previously on an ACE-inhibitor have a 36-hour washout period before initiation of sacubitril/valsartan to reduce risk of angioedema.[3,4]

Table 2: Target dose of sacubitril/valsartan in pediatric heart failure[4]

Population	Target Dose
Patients less than 40 kg	3.1 mg/kg twice daily
Patients at least 40 kg, less than 50 kg	72/78 mg twice daily
Patients at least 50 kg	97/103 mg twice daily

References:
1. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2017;136(6):e137-e161.
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Vericiguat (Verquvo®)

Goal(s):

- Restrict use of vericiguat in populations and at doses in which the drug has demonstrated efficacy.
- Encourage use of beta-blockers and inhibitors of the renin-angiotensin-aldosterone system with demonstrated evidence of mortality reduction in heart failure with reduced ejection fraction.

Length of Authorization:

- 6 to 12 months

Requires PA:

Vericiguat (Verquvo®)

Covered Alternatives:

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

Approval Criteria		
1. Is this a request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to Renewal Criteria	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code. Go to #3.	
3. Does the patient have symptomatic New York Heart Association (NYHA) Class II to IV chronic heart failure?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Does the patient have reduced ejection fraction (< 45%) assessed within the previous 12 months?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
5. Does the patient have worsening heart failure defined as one of the following? a. History of previous heart failure hospitalization within the last 6 months b. Intravenous diuretic use within previous 3 months	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the patient currently being seen by a cardiologist or heart failure specialist for management of advanced disease?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the patient on an angiotensin system inhibitor at maximally tolerated dose, such as: a. Angiotensin converting enzyme inhibitor (ACE-I) b. Angiotensin receptor blocker (ARB) c. Angiotensin receptor-neprilysin inhibitor (ARNI)	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Is the patient currently on a maximally tolerated dose of carvedilol, sustained-release metoprolol succinate, or bisoprolol; and if not, is there a documented intolerance or contraindication to each of these beta-blockers? *Note: the above listed beta-blockers have evidence for mortality reduction in chronic heart failure at target doses and are recommended by national and international heart failure guidelines.[1,2] Carvedilol and metoprolol succinate are preferred agents on the PDL.*	**Yes:** Go to #9	**No:** Pass to RPh. Deny, medical appropriateness
9. Is the patient on long-acting nitrates such as isosorbide dinitrate, isosorbide 5-mononitrate, transdermal nitroglycerin, or other similar agents or phosphodiesterase-5 (PDE5) inhibitors (e.g. sildenafil, tadalafil)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #10
10. Does the patient have stage 5 chronic kidney disease (eGFR < 15 ml/min or on hemodialysis/peritoneal dialysis)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for 6 months

Renewal Criteria		
1. Has the patient developed symptomatic hypotension or syncope while on vericiguat?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #2
2. Has the patient experienced disease progression, defined as either worsening NYHA functional class or worsening signs and symptoms of heart failure requiring intensification of therapy?	**Yes:** Go to #3	**No:** Approve for 12 months
3. Is the patient currently being seen by a cardiologist or heart failure specialist for management of advanced disease?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

References:
1. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;62(16):e147-239. doi: 10.1016/j.jacc.2013.05.019.
2. McMurray J, Adamopoulos S, Anker S, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. European Journal of Heart Failure. 2012;14:803-869. doi:10.1093/eurjhf/hfs105.

P&T / DUR Review: *06/21 (MH)*
Implementation: *TBD*

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Drug Class Update: Platelet Inhibitors

Date of Review: June 2021

Date of Last Review: September 2017
Dates of Literature Search: 07/01/2017 – 04/02/2021

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

Purpose for Class Update:
The purpose the class update is to evaluate new evidence on platelet inhibitors since the last review performed in 2017 and to ensure the preferred drug list (PDL) aligns with current evidence.

Research Questions:
1. Is there any new high-quality comparative evidence on the effectiveness of platelet inhibitors when used for stroke prevention, cardiovascular syndromes, prophylaxis for venous thromboembolism (VTE) or other indications?
2. Is there new high-quality comparative evidence on the harms of platelet inhibitors when used for stroke prevention, cardiovascular syndromes, prophylaxis for VTE or other indications?
3. Is there evidence regarding subgroups of patients based on demographics (age, racial groups, gender), socioeconomic status, other medications (drug-drug interactions), comorbidities (drug-disease interactions), or pregnancy for which a specific platelet inhibitor is more effective or associated with fewer harms than another platelet inhibitor?

Conclusions:
- A literature search up to April 2021 identified the following new evidence: 9 systematic reviews and meta-analyses, 6 guidelines, 1 randomized controlled trial (RCT), 1 safety alert and 2 new indications. The use of platelet inhibitors spans several different disease states, which includes multiple indications as outlined below.

<u>VENOUS THROMBOEMBOLISM</u>

- A high quality systematic review and meta-analysis in adult patients undergoing total hip replacement (THR) or total knee replacement (TKR) found moderate quality evidence that aspirin (ASA) was similar to other anticoagulants in venous thromboembolism (VTE) prevention (relative risk [RR] 1.12; 95% confidence interval [CI], 0.78 to 1.62).[1] These findings were supported by results of a recent Canadian Agency for Drugs and Technologies in Health (CADTH) Rapid Response Review.[2]

STROKE (Secondary prevention)

- A Cochrane review compared the efficacy and safety of multiple antiplatelets compared to fewer antiplatelets or multiple antiplatelets to one antiplatelet on prevention of recurrence in patients with recent ischemic stroke (type not specified) or transient ischemic attack (TIA) when treated for 3 months or longer.[3] The comparisons included the same trials except for one additional trial was included in the "multiple antiplatelet group" which studied ASA + clopidogrel + dipyridamole compared to ASA + dipyridamole or clopidogrel alone. All other trials studied two drug regimens compared to monotherapy.
    - For the comparison of multiple antiplatelets compared to fewer antiplatelets there was moderate to high quality evidence for the outcomes of stroke, ischemic stroke, myocardial infarction [MI], and the composite endpoint (e.g., stroke, vascular death or MI) that multiple antiplatelets were more effective.
    - For the comparison of dual antiplatelets to a single antiplatelet there was moderate to high quality of evidence that the use of dual antiplatelet therapy decreased the risk of stroke, ischemic stroke, and the composite endpoint (e.g., stroke, vascular death or MI).
    - There was high quality evidence that there was an increased risk of extracranial hemorrhage in patients treated with multiple antiplatelet therapies, treated for at least 3 months, compared to fewer antiplatelet therapies, 6.38% versus 2.81%, and for the comparison of dual antiplatelet therapies compared to single antiplatelet regimens, 1.24% versus 0.40%.[3]
- A high-quality systematic review and meta-analysis found that dual antiplatelet therapy with clopidogrel and ASA (75 mg to 300 mg), for up to 90 days, was more effective than ASA alone at reducing the risk of recurrent non-fatal stroke in patients with acute minor ischemic stroke or high risk TIA with an absolute risk reduction (ARR) of 1.9% (RR 0.70; 95% CI, 0.61 to 0.80) (high-quality of evidence).[4]

CARDIOVASCULAR EVENTS

- A 2019 CADTH review found moderate quality evidence that extended (treatment beyond 12 months) dual antiplatelet therapy (DAPT) treatment post-percutaneous coronary intervention (PCI) with stent placement (mostly drug eluting stents [DES]) was associated with a decreased risk of MI (number needed to treat [NNT] 174) and probable or definite stent thrombosis (NNT 348) compared to DAPT use of 6 to 12 months (standard of care). [5] There was an increase in non-CV death in participants treated with extended DAPT RR 2.15 (95% CI, 1.30 to 3.55) and no differences in major bleeding rates.
- A Cochrane review found moderate quality evidence of a reduced risk of fatal and non-fatal MI with ASA (75 mg to 325 mg) plus clopidogrel compared to ASA monotherapy (RR 0.78; 95% CI, 0.69 to 0.90) and fatal and non-fatal ischemic stroke (RR 0.73; 95% CI, 0.59 to 0.91) in patients with established cardiovascular (CV) disease (with or without MI) and without coronary stent.[6] Combination therapy was associated with an increased risk of major bleeding (RR 1.44; 95% CI, 1.25 to 1.64) and minor bleeding (RR 2.03; 95% CI, 1.75 to 2.36). Current data does not support routine use of the addition of clopidogrel to aspirin therapy in patients without coronary stents.
- A National Institute for Health and Care Excellence (NICE) guideline on acute coronary syndromes (ACS) are consistent with our current policy with a few exceptions.[7] NICE recommends the use of prasugrel for patients with acute STEMI. Patients with STEMI not treated with PCI should receive ticagrelor, with ASA. Patients with unstable angina or NSTEMI who are having coronary angiography, dual therapy with aspirin and either prasugrel or ticagrelor should be offered. Ticagrelor is indicated for patients, with aspirin, with unstable angina or NSTEMI when PCI is not recommended.
- A high-quality systematic review and meta-analysis in patients with a median baseline risk of a CV outcome of 10.2%, found ASA (75 mg to 100 mg) to reduce the risk of the primary composite CV outcome (CV mortality, nonfatal MI, and nonfatal stroke) more than no treatment (hazard ratio [HR] 0.89; 95% CI, 0.84 to 0.94; ARR 0.41%/NNT 241); however, ASA was also associated with an increased risk of major bleeding compared to no ASA (HR 1.43; 95% CI, 1.30 to 1.56; ARI 0.47%/NNH 210) and increased risk of intracranial hemorrhage was with ASA compared to no treatment (absolute risk increase [ARI] 0.11%/number needed to harm [NNH] 927) and major gastrointestinal [GI] bleeding (ARI 0.30%/NNH 334).[8]

PRE-ECLAMPSIA

- A Cochrane review found that the use of antiplatelet agents (aspirin 50-150 mg) reduced the risk of pre-eclampsia (number needed to benefit [NNTB] 61), preterm birth (NNTB 61), infant death (NNTB 197) and a reduction in infants small for gestational age (NNTB 146) compared to placebo in women at high risk of pre-eclampsia (mostly primary prevention trials started at different times of gestation).[9]
- There was insufficient high-quality evidence to make recommendations for the optimal use of platelet inhibitors in subgroup populations.

Recommendations:

- Update PA criteria to include new indications for ticagrelor.
- No changes to the PDL are warranted based on the evidence identified since the last review.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy:

- There were no changes made to the PDL as a result of the antiplatelet literature scan in 2017. Previous recommendations were to make clopidogrel, ASA and cilostazol preferred on the PDL.
- Evidence from previous reviews outline the importance of using DAPT following ACS, with evidence of decreased ischemic events with use beyond 12 months but with an increased risk of bleeding.
- Additional evidence was presented for prasugrel and ticagrelor that demonstrated a reduction in ischemic events compared to clopidogrel. A comparison between ticagrelor and clopidogrel found similar efficacy for prevention of CV outcomes and major bleeding.
- The risk of major adverse cardiovascular events (MACEs) was reduced more with prasugrel compared to clopidogrel but with a higher risk of bleeding.

Current Policy:

- Aspirin, ASA/dipyridamole, cilostazol, clopidogrel, and dipyridamole are preferred therapies. Non-preferred therapies require prior authorization (PA) to ensure platelet inhibitors are used for an approved diagnosis and patients are without contraindications.
- Ninety-nine percent of the utilization for this class is for preferred therapies. The overall spend for the antiplatelet class is not a significant source of resource allotment for the Oregon Health Authority (OHA).

Background:

The platelet inhibitor class is comprised of therapies that exert their effect via different mechanisms of action. Aspirin is the most commonly used antiplatelet which inhibits prostaglandin synthesis and platelet aggregation. The $P2Y_{12}$ inhibitors (e.g., clopidogrel, prasugrel, ticagrelor, ticlopidine) irreversibly block receptors which prevent adenosine diphosphate from activating platelets. Ticlopidine is not commonly used due to risk of life-threatening blood dyscrasias including thrombotic thrombocytopenic purpura (TTP), neutropenia/agranulocytosis and aplastic anemia, and is no longer available in the United States (US).[10] Less commonly used antiplatelets are cilostazol and dipyridamole. Cilostazol inhibits phosphodiesterase activity and subsequently suppresses cyclic adenosine monophosphate (cAMP) degradation leading to prevention of platelet aggregation, while dipyridamole exerts its effect by inhibiting adenosine uptake. Vorapaxar is the newest platelet inhibitor exerting its antiplatelet effect by selectively antagonizing the protease-activated receptor-1 (PAR-1).[11]

Platelet inhibitors are used for a several indications, including ACS (e.g., unstable angina, STEMI, and NSTEMI), peripheral arterial disease (PAD), stroke prevention, and less commonly as VTE prophylaxis. Both vorapaxar and prasugrel are contraindicated in patients with a history of stroke, TIA or intracranial

hemorrhage (ICH). The FDA approved indications are presented in **Table 1**. Outcomes used to determine efficacy and safety of platelet inhibitors include mortality, MI, stroke or TIA, VTE, CV death, stent thrombosis, minor bleeding and major bleeding.

Table 1. Antiplatelet FDA Approved Indications

Drug	Dose	Indication
Aspirin/extended-release dipyridamole[12]	25 mg aspirin/200 mg dipyridamole ER capsule twice daily	Reduction in stroke risk in patients who have had a TIA of the brain or completed ischemic stroke due to thrombosis
Clopidogrel[13]	300 mg single loading dose (if indicated) 75 mg daily (maintenance dose)	- ACS 1. Non-ST segment elevation ACS (unstable angina /NSTEMI). Reduction in the rate of MI and stroke 2. STEMI. Reduction has been shown to reduce the rate of MI and stroke. - Recent MI, recent stroke or established PAD with reduction in the risk of MI and stroke.
Cilostazol[14]	50 – 100 mg twice daily	Reduction of symptoms of intermittent claudication as demonstrated by an increased walking distance
Dypyridamole[15]	75 – 100 mg four times daily	Adjunct to coumarin anticoagulants in prevention of postoperative thromboembolic complications of cardiac valve replacement
Prasugrel[16]	5 – 10 mg once daily (aspirin 75-325 mg daily recommended)	- Reduction of thrombotic CV events (including stent thrombosis) in patients with ACS who are to be managed with PCI as follows: 1. Unstable angina or NSTEMI 2. STEMI when managed with either primary or delayed PCI
Ticagrelor[17]	60 – 90 mg twice daily (indication dependent maintenance dose)	- Reduction in the risk of CV death, MI and stroke in patients with ACS or history of MI - Reduction in the risk of stent thrombosis in patients who have been stented for the treatment of ACS - Reduction in the risk of first MI or stroke in patients with CAD at high risk for such events - Reduction in the risk of stroke in patients with acute ischemic stroke (NIH Stroke Scale $\leq$5) or high-risk TIA
Vorapaxar[11]	2.08 mg daily (with aspirin and clopidogrel)	Reduction of thrombotic CV events in patients with a history of MI or PAD. Reduction in the rate of the combined endpoint of CV death, MI, stroke, and urgent coronary revascularization.
Abbreviations: ACS – acute coronary syndrome; CAD – coronary artery disease; CV – cardiovascular; MI – myocardial infarction; NSTEMI - non-ST elevation MI; PAD – peripheral arterial disease; STEMI - ST-elevation MI; TIA – transient ischemic attack		

Guidelines recommend DAPT ($P2Y_{12}$ inhibitors in combination with ASA) for the management of ACS (for both STEMI and NSTEMI).[18,19] Platelet inhibition therapy is chosen for patients with STEMI based on reperfusion strategy. Prasugrel and ticagrelor are often preferred over clopidogrel for patients receiving PCI.[5] Clopidogrel has incomplete platelet inhibition resulting in a variable patient response. The American College of Cardiology/American Heart Association guidelines recommend duration of therapy to be determined by presence of stable coronary artery disease (CAD) in which 6 months is recommended or 12 months for patients with ACS. Use beyond 12 months is reserved for patients at high thrombotic risk and low risk for bleeding.[20] Aspirin use is often recommended to be continued indefinitely in patients with ACS. Guidelines no longer recommend ASA universally for primary prevention of cardiovascular disease but may be considered for patients with specific risk factors, such as diabetes.[21]

Atrial fibrillation (AF) without valvular heart disease is associated with a fivefold increase in incidence in stroke and subject to other underlying risk factors.[22] While AF is traditionally managed with anticoagulants, the use of a platelet inhibitor may occur when patients have comorbidities (e.g., ACS, stents, etc.) and require dual or triple therapy.[23] Clopidogrel, ASA or ASA/extended release (ER) dipyridamole are recommended for secondary prevention of non-cardioembolic ischemic stroke. Combination therapy with clopidogrel and ASA is used for patients with acute ischemic stroke and TIA as initial therapy, usually for 21 days; however, some studies continue treatment out to 90 days. Antiplatelets are also recommended in a subset of patients with valvular heart disease, in combination or in place of anticoagulants. In general, ASA 75 mg to 100 mg is recommended for this patient population.[24]

Symptomatic PAD patients can be managed with cilostazol. Aspirin or clopidogrel are recommended in patients with PAD who are at risk for CAD or stroke.

Methods:
A Medline literature search for new systematic reviews and RCT 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:

<u>VENOUS THROMBOEMBOLISM</u>
<u>CADTH – Acetylsalicylic Acid (Aspirin) for Venous Thromboembolism Prophylaxis in Hip and Knee Replacement</u>
A CADTH Rapid Response Report reviewed the evidence for the use of ASA as a prophylactic therapy in patients undergoing THR or TKR.[2] A literature search ranged from January 1, 2017 to July 22, 2020. Results of findings were reported independently and there was no meta-analysis of data due to heterogeneity of the trials. Five systematic reviews of randomized trials, fourteen non-randomized retrospective studies and one prospective study were included. Three guidelines were also included in the evidence recommendations. ASA was compared to LMWH (enoxaparin [40 mg once daily to 30 mg twice daily] and dalteparin [5000 units once daily]), Factor Xa inhibitors (rivaroxaban [10 mg daily], apixaban [2.5 mg]), direct thrombin inhibitor (dabigatran [220 mg]), warfarin

[initiated at 7.5 mg to 10 mg], or other anticoagulants. Treatment durations ranged from 9 days to 3 months and follow-up varied from 48 hours to one year. Patients were a mean range of 63-71 years and 18% to 44% were male. ASA doses ranged from 81 mg to 650 mg twice daily.[2]

Evidence for the use of ASA after THR or TKR found no significant differences in efficacy and safety between ASA and LMWH, Factor Xa inhibitors, direct thrombin inhibitors and warfarin.[2] Guidelines recommend the use of ASA for prophylaxis based on low quality of evidence. Additional high quality evidence is needed to recommend ASA over other anticoagulants for prophylaxis of VTE for most patients undergoing THR or TKR.

Matharu, et al – Clinical Effectiveness and Safety of Aspirin for VTE Prophylaxis after Total Hip and Total Knee Replacement

A 2020 systematic review and meta-analysis evaluated randomized controlled trial (RCTs) for evidence of efficacy and safety of using ASA (81 mg daily to 1500 mg twice daily) for prophylaxis in patients after they undergo a THR or TKR.[1] Thirteen RCTs (n=6060) with active treatment comparisons were included. Comparators were rivaroxaban (10 mg) with or without LMWH (4000 U daily), dalteparin (4000-50000 U daily), enoxaparin (40 mg daily warfarin (7.5 mg to 10 mg daily and titrated to target INR), LMW dextran (500 ml daily) and dipyridamole (400 mg daily). Treatment lengths ranged from 5 to 42 days. Participants were adults (18 years and older), 57.2% were women, and the mean age was 60.0 years. Of the 13 trials, 11 were open-label and 2 were double-blind.[1] Two studies had low risk of bias and 11 had a high risk of bias due to detection and performance bias. The primary outcome was the incidence of postoperative VTE (asymptomatic or symptomatic) and risk of bleeding.

Pooled results from 13 trials found the risk of ASA as a prophylactic therapy after THR and TKR to be similar to other anticoagulants (RR 1.12; 95% CI, 0.78 to 1.62) based on moderate quality evidence.[1] For the comparison of risk of DVT with ASA to other anticoagulants the results were similar (RR 1.04; 95% CI, 0.72 to 1.51) and for PE (RR 1.01; 95% CI, 0.68 to 1.48), based on moderate and high quality evidence, respectively. The risk of any bleeding was not different between ASA and other anticoagulants (RR 1.35; 95% CI, 0.73 to 2.49) or major bleeding (RR 1.11; 95% CI, 0.47 to 2.59). Evidence for the risk of adverse events was based on 2 trials and was considered low quality evidence.[1]

The review was limited by high heterogeneity across the studies; however, subgroup analyses suggested that the findings were consistent even with differing surgeries, comparative therapy and trial design. There was a high risk of bias found in many of the included studies which lowers the confidence in the findings. The authors had minor conflicts of interest resulting in a risk of bias. Additional, well-designed RCTs would further define the role of ASA as a prophylactic therapy in patients undergoing TKR and THR.

CARDIOVASCULAR EVENTS

Cochrane – Clopidogrel plus Aspirin versus Aspirin Alone for Preventing Cardiovascular Events

Cochrane updated a 2011 review on the benefits and risks of ASA therapy for preventing CV events in patients with established coronary disease, ischemic cerebrovascular disease, PAD or at high risk of atherothrombotic disease but did not have a coronary stent.[6] The updated search was up to July 4, 2017, which identified 13 new studies, bringing the study inclusion total to 15 (n=33,970). All but one study used clopidogrel 75 mg and ASA doses ranged from 70 mg to 325 mg. Treatment durations ranged from 6 weeks to 3.4 years. For most domains, studies were at low risk of bias.[6]

There was no difference between ASA alone and the combination of ASA and clopidogrel for the outcome of CV mortality (RR 0.98; 95% CI, 0.88 to 1.10) based on moderate quality of evidence (7 trials).[6] Based on a median follow-up of 12 months, the risk of fatal and non-fatal MI (6 trials) occurred in 58 per 1000 patients treated with ASA compared to 45 per 1000 patients treated with combination therapy (RR 0.78; 95% CI, 0.69 to 0.90) (moderate quality of evidence). There was moderate evidence that the risk of fatal and non-fatal ischemic stroke (5 trials) was less with combination therapy compared to ASA alone (RR 0.73;

95% CI, 0.59 to 0.91).[6] Evidence for all-cause mortality (9trials) was of low quality and found no difference between treatments. The risk of major bleeding (10 trials) was higher in patients treated with combination therapy compared to ASA alone (RR 1.44; 95% CI, 1.25 to 1.64) (moderate quality of evidence). Moderate evidence also found an increased risk of minor bleeding (8 trials) with combination therapy, 32 per 1000 patients treated compared to 65 per 1000 patients treated with ASA alone (RR 2.03; 95% CI, 1.75 to 2.36).[6]

Zheng, et al – Association of Aspirin Use for Primary Prevention with Cardiovascular Events and Bleeding Events

A high-quality systematic review and meta-analysis was published in 2019 on the use of aspirin and the corresponding benefits and risks when used for primary prevention in patients with a median baseline risk of a CV outcome of 10.2%,.[8] Aspirin was compared to placebo in 9 trials and no ASA in 4 studies. The ASA dose was 75 mg to 100 mg daily in 9 of the RCTS. A search up to November 1, 2018 identified 13 RCTs involving 164,225 participants.[8] The mean duration of follow-up was 5 years and 47.2% of participants were men. Studies enrolling just patients with diabetes were identified in 3 trials comprising 18.5% of patients. Four studies were at high risk of bias (open-label) with the remaining 9 being at low risk of bias (double-blind). The primary outcome was a composite of CV mortality, nonfatal MI, and nonfatal stroke. All-cause mortality, CV-related mortality, MI, total stroke (ischemic, hemorrhagic and unknown), and ischemic stroke were secondary outcomes. Major bleeding was the primary safety outcome, with secondary outcomes being intracranial bleeding and major GI bleeding.

The results for the primary composite CV outcome demonstrated a reduction with the use of ASA, 60 events per 10,000 participant-years, compared to no aspirin, 65.2 events per 10,000 participant-years (HR 0.89; 95% CI, 0.84 to 0.94; ARR 0.41%/NNT 241).[8] The incidence of all-cause mortality was not reduced with ASA compared to no therapy (HR 0.94; 95% CI, 0.88 to 1.01; ARR 0.13%).[8] The incidence of MI was reduced with ASA compared to no therapy by an ARR of 0.28% and NNT of 361. Aspirin reduced the risk of ischemic stroke by an ARR of 0.19% and NNT of 540.[8] Total stroke risk was not reduced by ASA therapy compared to no therapy (HR 0.93; 95% CI, 0.86 to 1.02). In a subgroup analysis of patients where CV risk was low, ASA reduced risks more than no treatment (ARR 0.63%/NNT 160). Results were the same for the risk in patients with a high risk of the CV outcome (ARR 0.63%/NNT 160).[8] The largest reduction in risk was in patients with diabetes where ASA reduced the primary composite CV outcome more than no treatment (HR 0.90; 95% CI, 0.82 to 1.00; ARR 0.65%/NNT 153).[8]

Major bleeding was increased with ASA, 23.1 events per 10,000 participant-years, compared to no treatment, 16.4 events per 10,000 participant-years (HR 1.43; 95% CI, 1.30 to 1.56; ARI 0.47%/NNH 210).[8] The incidence of intracranial hemorrhage was higher with ASA compared to no treatment (ARI 0.11%/NNH 927) and major GI bleeding (ARI 0.30%/NNH 334).[8]

The use of ASA in patients without CV disease was associated with less CV outcomes but higher rates of major bleeding, intracranial hemorrhage and major GI bleeds. The quality of the systematic review was limited by no list of studies that were excluded, omission of funding source and lack of inclusion of grey literature.

CADTH – Dual Antiplatelet Therapy Following Percutaneous Coronary Intervention: Clinical and Economic Impact of Standard Versus Extended Duration

A 2019 clinical effectiveness review done by CADTH evaluated the safety and efficacy of using DAPT (combination of $P2Y_{12}$ inhibitor [e.g., clopidogrel, prasugrel or ticagrelor] and aspirin), after PCI with stent insertion, as extended therapy (beyond 12 months) compared to the standard of practice duration of 6-12 months.[5] There were 8 RCTs (n=11,648) that met inclusion criteria and 7 were open-label. Additionally, evidence to guide the use of a particular $P2Y_{12}$ inhibitor was sought, but there was insufficient evidence to inform conclusions since most of the trials studied clopidogrel or a combination of $P2Y_{12}$ inhibitors. The mean patient age was 60 years A majority of patients had DES with only limited data on patients with bare-metal stent (BMS). All-cause, CV and non-cardiovascular death were all primary outcomes. Secondary outcomes of the review were MI, stroke, stent thrombosis, urgent target vessel revascularization, major adverse

cardiac and cerebrovascular event (MACCE), and bleeding. Trials were considered to be at low risk of bias. Trial bias was not downgraded for being open-label because outcomes were objective.[5]

Results for the primary and secondary outcomes are presented in **Table 2**.[5] Of interest was that the incidence of non-cardiovascular death was higher with patients treated with extended DAPT. Analysis of subgroup populations found that those patients with a history of MI had a reduced risk of subsequent MI, probable or definite stent thrombosis and MACCE when treated with extended therapy. Patients presenting with ACS also demonstrated a reduced risk of MI and probable or definite stent thrombosis with extended therapy. Those patients with diabetes were not found to have benefit with extended DAPT and may have an increased risk of bleeding. There was an increased risk of death among patients with no MI history and an increased risk of stroke in those over the age of 75 with extended DAPT therapy.[5] Smokers and non-smokers were found to have a reduced risk of MI and definite or probable stent thrombosis with extended duration of therapy. No trials studied used ticagrelor and only a few studies evaluated the use of prasugrel. Limitations to the evidence include different times of randomization from stenting to trial extended DAPT trial enrollment, and different definitions of MACCE and major bleeding.

Table 2. CADTH Review on the Use of Extended Duration DAPT versus Standard of Care[5]

Outcomes	Result	Comments
Myocardial Infarction (6 trials, N= 24,534)	RR 0.58 (95% CI, 0.48 to 0.70) NNT 174	Extended duration DAPT reduced the risk of MI compared to standard of care*
Probable or Definite Stent Thrombosis (5 trials, N = 19,489)	RR 0.38 (95% CI, 0.21 to 0.67) NNT 348	Extended duration DAPT reduced the risk of stent thrombosis compared to standard of care*
All-cause Death (7 trials, N = 25,982)	RR 1.07 (95% CI, 0.80 to 1.42)	No difference in risk of death between standard of care and extended DAPT therapy
Cardiovascular Death (5 trials, N = 21,561)	RR 0.98 (95% CI, 0.74 to 1.30)	No difference in risk of CV death between standard of care and extended DAPT therapy
Non-cardiovascular Death (3 trials, N = 14,666)	RR 2.15 (95% CI, 1.30 to 3.55)	Higher risk of death with extended DAPT compared to standard of care
Stroke (6 trials, N = 24,534)	RR 0.94 (95% CI, 0.70 to 1.25)	No difference in risk of stroke between standard of care and extended DAPT therapy
Urgent Revascularization (2 trials, N = 3,136)	RR 0.60 (95% CI, 0.24 to 1.54)	No difference in risk of urgent revascularization between standard of care and extended DAPT therapy
MACCE (5 trials, N = 21,227)	RR 0.95 (95% CI, 0.76 to 1.19)	No difference in risk of MACCE between standard of care and extended DAPT therapy
Major Bleeding† (4 trials, N = 9,579)	RR 1.42 (95% CI, 0.88 to 2.29)	No difference in the risk of major bleeding between standard of care and extended DAPT
Abbreviations: CV – cardiovascular death; DAPT – dual antiplatelet therapy; MACCE – major adverse cardiac and cerebrovascular event; NNT- number needed to treat; RR – relative risk; Key: * DAPT for 6-12 months; † As defined by thrombolysis in myocardial infarction (TIMI)		

STROKE

Cochrane – Multiple Versus Fewer Antiplatelet Agents for Preventing Early Recurrence After Ischemic Stroke or Transient Ischemic Attack

A 2020 Cochrane review evaluated the safety and efficacy of using fewer versus multiple antiplatelet therapies within 72 hours after a stroke or TIA, with continued treatment of 30 days to 3.5 years.[3] Fifteen studies (n=17,091) met inclusion criteria. Therapies included combinations of the following oral therapies: aspirin, clopidogrel, dipyridamole, cilostazol, thienopyridine, triflusal, buflomedil and sarpogrelate (the last four products are not available in the US). The most common combinations studied were clopidogrel plus aspirin and dipyridamole plus aspirin. Comparisons were considered to be "multiple antiplatelets" versus "fewer antiplatelets" was the combination of A+B+C versus C or A+B. "Multiple antiplatelets" versus "single antiplatelets" was the combination of the following A+B versus A or B. The primary outcome was stroke or vascular death 3 or more months after initiation of treatment.[3] Two trials were at high risk of bias and performance bias was high in 6 of the 15 trials, due to blinding issues. Results of findings for the comparison of "multiple antiplatelets" compared to "fewer antiplatelets" are presented in **Table 3**. Results for "multiple antiplatelets" compared to "single antiplatelet" are presented in **Table 4**.

Table 3. Multiple Antiplatelets Compared to Fewer Antiplatelets for Recurrence Prevention in Patients with Ischemic Stroke and Transient Ischemic Attacks[3]

Outcome at ≥3 months	Result	Quality of Evidence	Comments
Stroke	RR 0.73 (95% CI, 0.66 to 0.82)	Moderate	There were 22 *fewer* strokes per 1000 patients treated in patients receiving multiple agents versus fewer agents
Vascular Death	RR 0.98 (95% CI, 0.67 to 1.45)	Moderate	There was no difference between treatments
Myocardial Infarction (MI)	RR 1.38 (95% CI, 0.63 to 2.99)	High	There was no difference between treatments
Stroke, vascular death or MI	RR 0.72 (95% CI, 0.64 to 0.82)	Moderate	There were 25 *fewer* strokes, vascular deaths or MIs per 1000 patients treated in patients receiving multiple agents versus fewer agents
Intracranial hemorrhage	RR 1.92 (95% CI, 1.05 to 3.50)	Low	Low quality evidence prevents strong conclusions
Extracranial hemorrhage	RR 2.14 (95% CI, 1.79 to 2.57)	High	There were 36 *more* extracranial hemorrhages per 1000 patients treated in patients receiving multiple agents versus fewer agents
Ischemic Stroke	RR 0.73 (95% CI, 0.64 to 0.83)	High	There were 21 *fewer* ischemic strokes per 1000 patients treated in patients receiving multiple agents versus fewer agents
Abbreviations: CI – confidence interval; RR – relative risk			

Table 4. Multiple Antiplatelets Compared to One Antiplatelet for Recurrence Prevention in Patients with Ischemic Stroke and Transient Ischemic Attacks[3]

Outcome at ≥3 months	Result	Quality of Evidence	Comments
Stroke	RR 0.71 (95% CI, 0.62 to 0.80)	Moderate	There were 23 *fewer* strokes per 1000 patients treated in patients receiving dual antiplatelets versus one antiplatelet
Vascular Death	RR 0.84 (95% CI, 0.54 to 1.30)	Moderate	There was no difference between treatments
Myocardial Infarction (MI)	RR 1.38 (95% CI, 0.63 to 2.99)	High	There was no difference between treatments
Stroke, vascular death or MI	RR 0.72 (95% CI, 0.64 to 0.82)	Moderate	There were 25 *fewer* strokes, vascular deaths or MIs per 1000 patients treated in patients receiving dual antiplatelets versus one antiplatelet
Intracranial hemorrhage	RR 1.53 (95% CI, 0.76 to 3.06)	Low	Low quality evidence prevents strong conclusions
Extracranial hemorrhage	RR 3.08 (95% CI, 1.74 to 5.46)	High	There were *more* extracranial hemorrhages in patients receiving dual antiplatelets versus one antiplatelet
Ischemic Stroke	RR 0.70 (95% CI, 0.61 to 0.81)	High	There were 27 *fewer* ischemic strokes per 1000 patients treated in patients receiving dual antiplatelets versus one antiplatelet
Abbreviations: CI – confidence interval; RR – relative risk			

Hao, et al – Clopidogrel Plus Aspirin Versus Aspirin Alone for Acute Minor Ischemic Stroke or High Risk Transient Ischemic Attack

In a high-quality systematic review and meta-analysis the efficacy and safety of dual therapy with clopidogrel and aspirin compared to ASA alone was compared for the prevention of recurrent thrombotic and bleeding events in patients with minor ischemic stroke (National Institute of Health Stroke Scale [NIHSS] of 3 or less) or high risk TIA ($ABCD^2$ score of 4 or greater).[4] Literature search ranged from January 2012 to July 2018. Three trials met inclusion criteria including 1,447 participants which were enrolled within 12 or 24 hours of symptom onset. All trials used a loading dose of clopidogrel (300-600 mg) plus aspirin (75 mg to 300mg) compared to ASA (50 mg to 325 mg daily).[4] Trials were studied out to 90 days. Fifty-eight percent of participants were men and the average age was 65 years. All trials were found to be at an overall low risk of bias. Outcomes were non-fatal recurrent stroke (both ischemic and hemorrhagic), all-cause mortality, major or moderate non-fatal extracranial hemorrhage.

The risk of non-fatal recurrent stroke was reduced with dual antiplatelet therapy, compared to ASA alone, with an ARR of 1.9% (RR 0.70; 95% CI, 0.61 to 0.80) (high-quality of evidence).[4] The risk of non-fatal ischemic stroke was reduced more with dual therapy compared to ASA alone (RR 0.69; 95% CI, 0.60 to 0.79/ARR 2.0%) based on high-quality of evidence.[4] The incidence of non-fatal intracranial hemorrhage was increased with dual therapy compared to ASA (RR 1.27; 95% CI, 0.55 to 2.89) (moderate quality of evidence). Moderate quality evidence found no differences between treatment for the outcome of all-cause mortality (RR 1.27; 95% CI, 0.73 to 2.23).[4] The risk of moderate or major extracranial hemorrhage was increased with dual antiplatelet therapy with a RR of 1.71 (95% CI, 0.92 to 3.20), with an incidence of 3 per 1000 patient years with ASA compared to 5 per 1000 for patients treated with DAPT (ARR 0.2%) based on moderate quality of evidence.[4]

Study results were limited by differing loading doses of both clopidogrel and ASA. Only three trials met inclusion criteria and therefore, additional evidence would strengthen the conclusions. The quality of the systematic review and meta-analysis had appropriate methods with no funding conflicts or authors with conflicts of interest.

PRE-ECLAMPSIA

Cochrane – Antiplatelet Agents for Preventing Pre-eclampsia and Its Complications

A 2019 Cochrane review evaluated the evidence for antiplatelet (e.g., aspirin and dipyridamole) use on the risk of development of pre-eclampsia.[9] Seventy-seven trials were included, although most of the data was contributed from 9 larger trials. The use of ASA, in doses ranging from 50 mg to 150 mg, was the most common treatment studied. Women included in the study were considered to be at high risk of developing preeclampsia and most trials were primary prevention trials. Gestational age varied at time of antiplatelet initiation. The incidence of pre-eclampsia in the trials varied substantially from 2% to 60%. Overall quality of the trials was considered to be good, with most trials having a low risk of bias.

High quality evidence found reduced proteinuric pre-eclampsia in women taking antiplatelets compared to placebo, 16 fewer per 1000 versus 92 per 1000 (RR 0.82; 95% CI, 0.77 to 0.88: NNTB 61).[9] Infant death was 27per 1000 in the antiplatelet group compared to 33 per 1000 in the placebo group (RR 0.85; 95% CI, 0.76 to 0.95) (high quality evidence). Preterm birth, defined as birth before 37-weeks gestation, was less in women taking antiplatelets with a RR 0.91 (95% CI, 0.87 to 0.95; NNTB 61) based on high quality of evidence.[9] There was high quality evidence that women given antiplatelets had a risk of infants that were small for gestational age, 40 per 1000, compared to placebo risk, 47 per 1000 (RR 0.84; 95% CI, 0.76 to 0.92; NNTB 146).[9] The risk of postpartum hemorrhage was not statistically different in women treated with antiplatelets compared to placebo (RR 1.06; 95% CI, 1.00 to 1.12). Moderate quality evidence found trials reporting individual patient data evaluated serious adverse events outcome (composite of material death, baby death, pre-eclampsia, small-for-gestational age, preterm birth) found 177 per 1000 in women treated with antiplatelets compared to 197 per 1000 for placebo (NNTB 54) (high quality evidence).[9] There was moderate evidence that the risk of postpartum hemorrhage (>500 ml) was slightly increased with antiplatelet therapy (RR 1.06; 95% CI, 1.00 to 1.12).

There was small to moderate benefit for the use of aspirin in women at risk of pre-eclampsia. Outcomes that saw the most benefit were a reduction in risk for proteinuric pre-eclampsia, preterm birth, and infant death.

After review, 70 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).[25–34, 35–44, 45–54, 31,55–63, 64–73, 74–83, 46,84–93]

New Guidelines:

High Quality Guidelines:

NICE – Acute Coronary Syndromes

In November 2020 NICE updated guidance on the use of antiplatelets in coronary syndromes.[7] Early management of acute STEMI or NSTEMI and unstable angina includes administration of 300 mg aspirin unless there is a clear allergy. Patients with acute STEMI who are having a primary PCI should be offered prasugrel, in addition to aspirin, if no other anticoagulant is being taken. Patients already taking an anticoagulant should be offered clopidogrel.[7] Patients with STEMI not treated with PCI should be offered ticagrelor, in combination with ASA. Clopidogrel should be used if there is a high risk of bleeding.

For patients with unstable angina and NSTEMI intended for PCI, ticagrelor has the most evidence for use.[7] NICE also recommends the use of ticagrelor in patients not having coronary revascularization or coronary artery surgery. For patients at high risk of bleeding, clopidogrel may be a better option. For patients with unstable angina or NSTEMI who are having coronary angiography, dual therapy with aspirin and either prasugrel or ticagrelor should be offered. Clopidogrel

should be given if the patient has an indication for ongoing oral anticoagulation. Ticagrelor is indicated for patients, with aspirin, with unstable angina or NSTEMI when PCI is not recommended. If there is a high risk of bleeding clopidogrel is recommended with ASA, or ASA use alone.[7]

Patients that have had a MI, dual antiplatelet therapy with ASA and one other antiplatelet is recommended for secondary prevention for at least 12 months. Aspirin is recommended indefinitely unless there is a contraindication. If the patient cannot take ASA or if they have clinical vascular disease, clopidogrel monotherapy is an alternative option. If the patient has a separate indication for anticoagulation continue clopidogrel for up to 12 months.[7]

NICE – Venous Thromboembolic Diseases: Diagnosis, Management and Thrombophilia Testing

A 2020 guidance from NICE included recommended anticoagulant therapy for the management of VTE.[94] Antiplatelet therapy (e.g., ASA), as it pertains to this update, will be the reported. Additional anticoagulant recommendations will be included in that designated update. The role of ASA (75 mg to 150 mg daily) is recommended by the guidance for use in patients who require long-term anticoagulation for secondary prevention in patients who decline anticoagulation.[94] No other recommendations pertaining to ASA were included in the guidance.

Additional Guidelines for Clinical Context:

AHA/ACC/HRS Focused Update of the 2014 Guideline on the Management of Patients with Atrial Fibrillation

In 2019 the American Heart Association (AHA)/American College of Cardiology (ACC)/ Heart Rhythm Society (HRS) updated guidance on AF management.[22] A significant portion of the professional practice committee members had conflicts with industry and associations themselves funded by industry. The guideline will be included for clinical context. Pharmacologic recommendations, pertaining to antiplatelet therapy, will be discussed. Recommendations are given a class (strength) of recommendation and level (quality) of evidence recommendation. The class of recommendation range from weak to strong (**Table 5**) and level of evidence description in **Table 6**.

The management of patients with AF is often complicated by the presence of comorbidities. The recommendations for ACS are for dual antiplatelet therapy (DAPT), with the addition of warfarin or novel oral anticoagulants (NOAC) for triple therapy in patients with AF at increased risk of stroke (**Table 7**).[22] The recommendations for the use of ASA have been updated from findings of recent trials showing less benefit of ASA for primary prevention than originally thought. Evidence still strongly supports the use of ASA for secondary prevention of atherosclerotic cardiovascular disease (ASCVD).

Table 5. Description of Class of Recommendation Description[22]

Class of Recommendation	Description
Class I (Strong)	Benefit >>> Risk
Class IIa (Moderate)	Benefit >> Risk
Class IIb (Weak)	Benefit ≥ Risk
Class III: No Benefit (Moderate)	Benefit = Risk
Class III: Harm (Strong)	Risk > Benefit

Table 6. Level of Evidence Description[22]

Level of Evidence	Description
Level A	High quality evidence from more than one RCT Meta-analysis of high quality RCTs One or more RCT corroborated by high-quality registry studies
Level B-R (Randomized)	Moderate quality evidence from 1 or more RCTs Meta-analyses of moderate-quality RCTs
Level B-NR (Nonrandomized)	Moderate quality evidence from 1 or more well-designed nonrandomized studies, observational, or registry studies Meta-analyses of such studies
Level C-LD (Limited data)	Randomized or nonrandomized trials with limitations Meta-analyses of such studies Physiological or mechanistic studies in human subjects
Level C-EO (Expert opinion)	Consensus of expert opinion based on clinical experience

Table 7. Recommendations for the Use of Antiplatelet Therapy in Patients with Atrial Fibrillation[22]

Recommendation	Class of Recommendation	Level of Evidence
AF Complicating ACS		
Clopidogrel is recommended over prasugrel in patients who are prescribed triple therapy with AF at increased risk of stroke who have undergone PCI with stenting for ACS	IIa	B-NR
Dose-adjusted vitamin K antagonist with a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor) is a reasonable option in patients with AF at increased risk of stroke who have undergone PCI with stenting for ACS	IIa	B-R
Low-dose rivaroxaban (15 mg) daily with a $P2Y_{12}$ inhibitor (clopidogrel) is a reasonable option to reduce the risk of bleeding in patients with AF at increased risk of stroke who have undergone PCI with stenting for ACS	IIa	B-R
Double therapy with a $P2Y_{12}$ inhibitor (clopidogrel) and dabigatran 150 mg twice daily is reasonable to reduce the risk of bleeding compared to triple therapy in patients with AF at increased risk of stroke who have undergone PCI with stenting for ACS	IIa	B-R
If triple therapy (oral anticoagulant, $P2Y_{12,}$ and aspirin) is prescribed in patients with AF at increased risk of stroke who have undergone PCI with stenting for ACS, a transition to double therapy (oral anticoagulant and $P2Y_{12}$ inhibitor) at 4-6 weeks may be considered.	IIb	B-R
Aspirin Use		
Low-dose aspirin (75 mg to 100 mg) may be considered for primary preventions of ASCVD among certain adults 40-70 years old or at higher ASCVD risk but not at increased bleeding risk	IIb	A
For patients 70 years and older, low-dose aspirin (75 mg to 100 mg) should not be administered on a regular basis for the primary prevention of ASCVD	III: Harm	B-R
For adults at increased risk of bleeding the daily administration of low-dose aspirin (75 mg to 100 mg) should not be administered for the primary prevention of ASCVD	III: Harm	C-LD
Abbreviations: ACS - acute coronary syndrome; AF – atrial fibrillation; ASCVD – atherosclerotic cardiovascular disease		

ACC/AHA – Guideline on the Primary Prevention of Cardiovascular Disease

General guidelines for the primary prevention of CV disease in adults was published in 2019 by ACC/AHA.[21] See limitations to the guidelines as discussed above. The class of recommendation and level of evidence description are described above (**Tables 5 and 6**). Recommendations pertaining to management of diabetes, hypertension and lipids will be reviewed in another class update. Aspirin for primary prevention was recommended for a select group of patients as described in the AF Guideline above in **Table 7**.

ACC/AHA – Guideline for the Management of Patient with Valvular Heart Disease

The ACC/AHA updated guidance in 2020 for the management of patients with valvular heart disease.[24] This guideline also had the same class of recommendation and level of evidence designation as the previous 2 guidelines with detailed descriptions in **Tables 5 and 6**, as well as the same limitations as discussed above. The literature was searched from January 1, 2010 to March 1, 2020. Anticoagulation with a vitamin K antagonist (VKA) is most often recommended to patients with prosthetic valves. The use of antiplatelet therapy is an option as described below in **Table 9**.

Table 9. Antiplatelet Use in the Management of Patients with Prosthetic Valves[24]

Recommendation	Class of Recommendation*	Level of Evidence
Aspirin 75 mg to 100 mg daily is reasonable for patients with bioprosthetic TAVI and the absence of other indications for oral anticoagulants	2a	B-R
Aspirin 75 mg to 100 mg daily is reasonable for patients with bioprosthetic SAVR or mitral valve replacement and in the absence of other indications for oral anticoagulants	2a	B-NR
Aspirin 75 mg to 100 mg daily, in addition to a VKA, may be considered for patients with a mechanical SAVR or mitral valve replacement who have an indication for antiplatelet therapy when the bleeding risk is low	2b	B-R
Patients should be continued on ASA 75 mg to 100 mg and may have consider a VKA targeted to a lower INR (1.5 – 2.0) 3 or more months after surgery that have a mechanical On-X AVR and no thrombotic risk factors	2b	B-NR
Aspirin 75 mg to 100 mg and clopidogrel 75 mg may be reasonable 3-6 months after valve implementation for patients with bioprosthetic TAVI who are at low risk of bleeding	2b	B-NR
Low-dose rivaroxaban (10 mg daily) and aspirin 75 mg to 100 mg is contraindicated in the absence of other indications for oral anticoagulants for patients with bioprosthetic TAVI	3: Harm	B-R
Abbreviations: ASA – aspirin; AVR – aortic valve replacement; INR - international normalized ratio; TAVI – transcatheter aortic valve implantation; SAVR – surgical aortic valve replacement; VKA – vitamin K antagonist Key: * The class of recommendation designations were changed from Roman Numeral to numbers in 2020 guidelines but are identically defined.		

In patients who have had thromboembolic events with prosthetic valves (mechanical and bioprosthetic), the addition of antiplatelet therapy is recommended. In patients who have had a stroke or systemic embolic event while in therapeutic range on VKA anticoagulation with a mechanical AVR or mechanical mitral valve replacement, it is reasonable to increase the INR goal from 2.5 (range 2.0 to 3.0) to 3.0 (range 2.5 to 3.5) or to add daily low-dose ASA (75 mg to 100 mg) with assessment of bleeding.[24] Patients who experience a thromboembolic event or stroke while on antiplatelet therapy with a bioprosthetic surgical or transcatheter

aortic valve or bioprosthetic mitral valve should be considered for VKA anticoagulation after assessment of bleeding risk. ASA 75 mg to 100 mg daily may be considered for pregnant women with mechanical valve prostheses, in addition to other anticoagulation, if needed for other indications.[24]

CHEST – Antithrombotic Therapy for Atrial Fibrillation

In 2018, CHEST updated guidance on the management of patients with AF.[23] Guidelines met criteria for inclusion with the limitations of having a majority of authors with conflicts with industry, including the chair. CHEST receives industry support which could bias clinical recommendations. The guideline will be included for context but not relied on for making policy decisions. The literature was searched from January 1, 2007 through October 2017. The quality of evidence was assessed using the GRADE approach, designations of strong to weak, and risk of bias was evaluated for randomized and nonrandomized trials. Anticoagulants are the mainstay of treatment in patients with AF; however, antiplatelets have a role in certain patient populations as described in **Table 10**.[23] Recommendations pertaining to anticoagulants were included in the corresponding class update.

Table 10. CHEST Guidance of the Use of Antiplatelet Therapies in Patients with Atrial Fibrillation[23]

Recommendation	Strength of Recommendation	Quality of Evidence
Antiplatelet therapy alone (monotherapy or ASA in combination with clopidogrel) is not recommended for patients with AF for stroke prevention alone, regardless of stroke risk	Strong	Moderate
Triple therapy for 1-3 months followed by dual therapy with an OAC plus a single antiplatelet (preferably clopidogrel) for 6 months, followed by OAC monotherapy is recommended for patients with AF requiring OAC undergoing elective PCI/stenting where bleeding risk is low (HAS -BLED 0-2) compared to risk for recurrent ACS and/or stent thrombosis	Weak	Low
Triple therapy for 1 month, followed by dual therapy with OAC plus an antiplatelet (preferably clopidogrel) for 6 months, following which OAC monotherapy is recommended for patients with AF requiring OAC undergoing elective PCI/stenting where bleeding risk is high (HAS -BLED $\geq$3) compared to risk for recurrent ACS and/or stent thrombosis	Weak	Low
OAC plus a single antiplatelet (preferably clopidogrel) for 6 months, followed by OAC monotherapy is recommended in patients with AF requiring OAC undergoing elective PCI/stenting where bleeding risk unusually high and thrombotic risk is unusually low	Weak	Low
Triple therapy for 6 months followed by dual therapy with OAC plus a single antiplatelet (preferably clopidogrel) until 12 months following which OAC monotherapy is recommended with patients with AF requiring OAC presenting with ACS, undergoing PCI/stenting where bleeding risk is low (HAS -BLED 0-2) compared to risk for recurrent ACS or stent thrombosis	Weak	Low
Triple therapy for 1-3 months, followed by dual therapy with OAC plus single antiplatelet (preferably clopidogrel) up to 12 months, in which OAC monotherapy can be used for patients with AF requiring OAC presenting with ACS, undergoing PCI/stenting where bleeding risk is high (HAS -BLED $\geq$3) compared to risk for recurrent ACS and/or stent thrombosis	Weak	Low
OAC plus a single antiplatelet (preferably clopidogrel) for 6-9 months, followed by OAC monotherapy is recommended for patients with AF requiring OAC presenting with ACS, undergoing elective PCI/stenting where bleeding risk is unusually high and thrombotic risk is low	Weak	Low

If ASA is used with OAC in patients with AF, a dose of 75 mg to 100 mg daily is recommended with concomitant use of a PPI to minimize GI bleeding	Weak	Low
If a $P2Y_{12}$ inhibitor is used with an OAC in patients with AF then clopidogrel is recommended	Weak	Low
Abbreviations: ACS – acute coronary syndrome; AF – atrial fibrillation; ASA – aspirin; HAS – BLED – hypertension, abnormal renal/liver function (1 point), stroke, bleeding history or predisposition, labile INR, elderly (0.65), drugs/alcohol concomitantly (1 point each); OAC – oral anticoagulant therapy; PCI – percutaneous coronary intervention; PPI – proton pump inhibitor		

AHA/ASA – Guidelines for the Early Management of Patients with Acute Ischemic Stroke

In 2018 the AHA/ASA updated 2013 guidance on the management of patients with acute ischemic stroke.[95] This guideline had minimal authors with connection to industry. See **Table 5** and **6** for descriptions on the level of evidence grading and types of recommendations. A majority of the guideline pertained to non-pharmacologic management of stroke or use of pharmacotherapy not classified as antiplatelets. For the purpose of this update, just platelet inhibitors will be discussed in **Table 11**.

Table 11. Recommendations for the Use of Platelet Inhibitors for Acute Management of Ischemic Stroke[95]

Recommendation	Class of Recommendation	Level of Evidence
ASA should be administered with AIS within 24-48 hours after stroke onset. Delay administration 24 hours if patient received IV alteplase	I	A
ASA should not be used as a substitute for acute stroke treatment in patients who are otherwise eligible for IV alteplase or mechanical thrombectomy	III: No benefit	B-R
In patients with minor stroke, DAPT (ASA + clopidogrel) for 21 days begun within 24 hours can be beneficial for early secondary stroke prevention for a period of up to 90 days from symptom onset	IIa	B-R
Ticagrelor is not recommended over ASA for the acute treatment of patients with minor stroke	III: No benefit	B-R

After review, 5 guidelines were excluded due to poor quality.[88,95–98]

New Indications:

Brilinta® (Ticagrelor) – Obtained 2 new indications in 2020.

- The FDA approved ticagrelor (in combination with ASA) in May of 2020 for the indication of reducing the risk of first MI or stroke in patients with coronary artery disease at high risk for such event. Efficacy for use was established in patients with type 2 diabetes mellitus (T2DM), but is not limited to this patient population.[17]
- In November of 2020 the FDA approved ticagrelor to reduce the risk of stroke in patients with acute ischemic stroke (NIH Stroke Scale score of 5 or less) or high-risk transient ischemic attack (TIA).[17]

New FDA Safety Alerts:

Table 1. Description of new FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Ticagrelor[17]	Brilinta®	10/2019	Warnings and Precautions	Reported to cause false negative test results in platelet functional tests (to include, but not limited to, the heparin-induced platelet aggregation (HIPA) assay) for patients with Heparin Induced Thrombocytopenia (HIT)

Randomized Controlled Trials:

A total of 559 citations were manually reviewed from the initial literature search. After further review, 558 RCT 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). Abstracts are presented for included trials in Appendix 2.

Table 12. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
ACEND Study Collaborative Group[99]	1. Aspirin 100 mg daily 2. Placebo daily Mean follow-up of 7.4 years	Adult patients with diabetes (94% type 2) but no evidence of CV disease	First serious vascular event (i.e., MI, stroke, TIA or death from any vascular cause, excluding any confirmed intracranial hemorrhage)	Aspirin: 658 (8.5%) Placebo: 743 (9.6%) RR 0.88 (95% CI, 0.79 to 0.97) P=0.01 *Aspirin use reduced vascular events in participants with diabetes but increased major bleeding (benefits counterbalanced by bleeding hazard)*

Abbreviations: CV – cardiovascular; MI – myocardial infarction; RCT - randomized clinical trial, RR – rate ratio; TIA – transient ischemic attack

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Generic	Brand	Form	PDL
aspirin	ASPIRIN	TAB CHEW	Y
aspirin	CHILDREN'S ASPIRIN	TAB CHEW	Y
aspirin	ASPIRIN	TABLET	Y
aspirin	LITE COAT ASPIRIN	TABLET	Y
aspirin	ADULT ASPIRIN	TABLET DR	Y
aspirin	ADULT ASPIRIN REGIMEN	TABLET DR	Y
aspirin	ASPIR 81	TABLET DR	Y
aspirin	ASPIRIN	TABLET DR	Y
aspirin	ASPIRIN EC	TABLET DR	Y
aspirin	ASPIRIN EC	TABLET DR	Y
aspirin	ASPIR-LOW	TABLET DR	Y
aspirin	ECPIRIN	TABLET DR	Y
aspirin/dipyridamole	AGGRENOX	CPMP 12HR	Y
aspirin/dipyridamole	ASPIRIN-DIPYRIDAMOLE ER	CPMP 12HR	Y
cilostazol	CILOSTAZOL	TABLET	Y
clopidogrel bisulfate	CLOPIDOGREL	TABLET	Y
clopidogrel bisulfate	PLAVIX	TABLET	Y
dipyridamole	DIPYRIDAMOLE	TABLET	Y
aspirin/omeprazole	YOSPRALA	TAB IR DR	N
prasugrel HCl	EFFIENT	TABLET	N
prasugrel HCl	PRASUGREL HCL	TABLET	N
ticagrelor	BRILINTA	TABLET	N
ticlopidine HCl	TICLOPIDINE HCL	TABLET	N
vorapaxar sulfate	ZONTIVITY	TABLET	N

Appendix 2: Abstracts of Comparative Clinical Trials

Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus

ASCEND Study Collaborative Group; Louise Bowman, Marion Mafham, Karl Wallendszus, Will Stevens, Georgina Buck, Jill Barton, Kevin Murphy, Theingi Aung, Richard Haynes, Jolyon Cox, Aleksandra Murawska, Allen Young, Michael Lay, Fang Chen, Emily Sammons, Emma Waters, Amanda Adler, Jonathan Bodansky, Andrew Farmer, Roger McPherson, Andrew Neil, David Simpson, Richard Peto, Colin Baigent, Rory Collins, Sarah Parish, Jane Armitage

Abstract

Background: Diabetes mellitus is associated with an increased risk of cardiovascular events. Aspirin use reduces the risk of occlusive vascular events but increases the risk of bleeding; the balance of benefits and hazards for the prevention of first cardiovascular events in patients with diabetes is unclear.

Methods: We randomly assigned adults who had diabetes but no evident cardiovascular disease to receive aspirin at a dose of 100 mg daily or matching placebo. The primary efficacy outcome was the first serious vascular event (i.e., myocardial infarction, stroke or transient ischemic attack, or death from any vascular cause, excluding any confirmed intracranial hemorrhage). The primary safety outcome was the first major bleeding event (i.e., intracranial hemorrhage, sight-threatening bleeding event in the eye, gastrointestinal bleeding, or other serious bleeding). Secondary outcomes included gastrointestinal tract cancer.

Results: A total of 15,480 participants underwent randomization. During a mean follow-up of 7.4 years, serious vascular events occurred in a significantly lower percentage of participants in the aspirin group than in the placebo group (658 participants [8.5%] vs. 743 [9.6%]; rate ratio, 0.88; 95% confidence interval [CI], 0.79 to 0.97; P=0.01). In contrast, major bleeding events occurred in 314 participants (4.1%) in the aspirin group, as compared with 245 (3.2%) in the placebo group (rate ratio, 1.29; 95% CI, 1.09 to 1.52; P=0.003), with most of the excess being gastrointestinal bleeding and other extracranial bleeding. There was no significant difference between the aspirin group and the placebo group in the incidence of gastrointestinal tract cancer (157 participants [2.0%] and 158 [2.0%], respectively) or all cancers (897 [11.6%] and 887 [11.5%]); long-term follow-up for these outcomes is planned.

Conclusions: Aspirin use prevented serious vascular events in persons who had diabetes and no evident cardiovascular disease at trial entry, but it also caused major bleeding events. The absolute benefits were largely counterbalanced by the bleeding hazard. (Funded by the British Heart Foundation and others; ASCEND Current Controlled Trials number, ISRCTN60635500 ; ClinicalTrials.gov number, NCT00135226 .).

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to April 02, 2021
Search Strategy:

#	Searches	Results
1	aspirin.mp. or Aspirin/	68958
2	dipyridamole.mp.	10529
3	cilostazol.mp. or Cilostazol/	1942
4	clopidogrel.mp. or Clopidogrel/	15022
5	prasugrel.mp. or Prasugrel Hydrochloride/	2617
6	ticagrelor.mp. or Ticagrelor/	3174
7	ticlopidine.mp. or Ticlopidine/	11094
8	vorapaxar.mp.	339
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	88006
10	limit 9 to (english language and humans and yr="2017 -Current")	7623
11	limit 10 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	559

Appendix 4: Key Inclusion Criteria

Population	Patients with an indication for treatment with a platelet inhibitor
Intervention	Platelet inhibitors
Comparator	Placebo or active treatment comparison
Outcomes	Mortality, stroke, myocardial infarction, cardiovascular death, stent thrombosis, and thrombotic cardiovascular events
Timing	Treatment or prophylaxis (primary or secondary)
Setting	Inpatient or outpatient

Platelet Inhibitors ~~Antiplatelets~~

Goal:

- Approve antiplatelet drugs for funded diagnoses which are supported by medical literature.

Length of Authorization:

- Up to 12 months.

Requires PA:

- Non-preferred drugs

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis an OHP funded diagnosis?	**Yes:** Go to #3	**No:** Pass to RPh. Deny, not funded by the OHP.
3. Will the prescriber consider a change to a preferred product?	**Yes:** Inform provider of preferred alternatives.	**No:** Go to #4
4. Is this new therapy for a patient who was hospitalized and had an antiplatelet initiated in the hospital?	**Yes:** Approve for 30 days only and request a PA from the provider for continuation of therapy.	**No:** Go to #5

Approval Criteria		
5. Is this a request for continuation of therapy for a patient that already received 30 days of therapy that was initiated in the hospital?	**Yes:** Approve for FDA-approved indication for up to 1 year.	**No:** Go to #6
6. Is the request for ticagrelor?	**Yes:** Go to #7	**No:** Got to #8
7. Does the patient have a history of intracranial hemorrhage?	**Yes:** Deny for medical appropriateness	**No:** Approve for FDA-approved indication for up to 1 year.
~~7.~~8. Is the request for either prasugrel or vorapaxar AND does the patient have a history of stroke, TIA or intracranial hemorrhage?	**Yes:** Deny for medical appropriateness	**No:** Approve for FDA-approved indications for up to 1 year. If vorapaxar is requested, it should be approved only when used in combination with aspirin and/or clopidogrel. There is limited experience with other platelet inhibitor drugs or as monotherapy.

FDA Approved Indications (April 2021)

	1° Stroke	2° Stroke	2° PAD	1° MI	2° MI	ACS	
						No PCI	PCI
ASA/DP ER		x					
clopidogrel		x	x		x	x	x
prasugrel		CI					x
ticagrelor	x	x		x	x	x	x

vorapaxar		CI	x		x		

Abbreviations: 1 ^{o} = prevention, 2^{o} = secondary prevention; ACS=Acute Coronary Syndrome; ASA/DP ER = aspirin/dipyridamole; CI=contraindication; PCI=Percutaneous Intervention; X = FDA-approved indication.

P&T / DUR Review: *6/21 (KS), 9/17 (MH); 7/15; 11/11*
Implementation: *10/15, 8/15; 7/31/14; 4/9/12*

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Drug Use Evaluation: Migraine Prophylaxis

Research Questions:

1. How many patients in the Oregon fee-for-service (FFS) Medicaid population are prescribed triptans chronically for abortive migraine treatment?
2. What percentage of patients on chronic triptans are co-prescribed a guideline recommended migraine prophylactic agent?
3. How does use of a prophylactic agent affect triptan utilization, hospitalization, and emergency department (ED) visit rates for migraines?
4. How many patients have been prescribed a Calcitonin Gene-Related Peptide (CGRP) antagonist for migraine prophylaxis?
5. What are the most common reasons a CGRP antagonist claim or prior authorization (PA) request for migraine prophylaxis was denied?

Conclusions:

- Very few patients in the Oregon FFS Medicaid population are utilizing triptans chronically (N=113,228 total enrolled patients from Oct 2018 – Sept 2019; N=1,178 used at least one triptan; N=169 used triptans chronically).
- Of the patients using chronic triptans, about half (N=92, 54%) were also prescribed a guideline recommended prophylaxis agent. Guidelines would suggest that all of these patients would qualify for prophylaxis use.
- If a prophylaxis agent was initiated, the majority of patients (N=78, 85%) received an adequate trial of those agents. This suggests the primary barrier to appropriate prophylaxis use is initiation of therapy rather than continuation of use.
- No major conclusions could be drawn about the impact of prophylaxis use on hospitalization rates or ED visit rates given the small sample size and low number of ED visits and hospitalizations overall.
- Since the PA criteria for CGRP antagonists was implemented in Nov 2018, 525 unique claims were submitted for a CGRP antagonist with an indication for migraine prophylaxis, of which 257 (49%) were paid.
- The most common reason a claim for the prophylaxis CGRP antagonists was denied (N=268) is because it required a PA (N = 253, 94%). However, only 180 unique PAs were requested. What portion of these denied claims, if any, that would have met PA criteria if they had requested one is unknown. However, the majority of PAs that were requested were approved (N = 127, 71%).

Recommendations:

- No policy changes for triptan therapy are recommended at this time
- Consider provider education (such as continuing education or a brief pamphlet/newsletter) to increase migraine prophylaxis use in patients taking chronic triptans
- No PA criteria changes for CGRP antagonists are recommended at this time

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Current Policy:

- Oregon FFS Medicaid currently has the following quantity limits for preferred triptans to prevent medication overuse headaches. See **Appendix A** for a list of all triptans (preferred and non-preferred) and their respective quantity limits.

Table 1: Preferred Triptans and their Quantity Limits for Oregon FFS Medicaid[1]

Generic Name	Brand Name	Quantity Limit per Month
Naratriptan	Amerge®	9 tabs
Sumatriptan tablets	Imitrex® & generics	9 tabs
Sumatriptan nasal spray	Imitrex® & generics	18 spray units
Sumatriptan injectable	Imitrex® & generics	6 vials
Zolmitriptan tablets	Zomig® Zomig® ZMT	6 tabs
Zolmitriptan nasal spray	Zomig® NS	3 packages (18 spray units)
Abbreviations: NS – nasal spray; ZMT – zolmitriptan orally disintegrating tablet		

- Oregon FFS Medicaid currently has at least one formulation of the following guideline recommended migraine prophylactic agents (see **Table 3**) with a "preferred" designation: topiramate, propranolol, metoprolol (both tartrate and succinate formulations), divalproex sodium, valproic acid, amitriptyline, venlafaxine, and atenolol.
- Timolol and nadolol are the only recommended migraine prophylaxis agents with a "non-preferred" designation on the Oregon FFS Medicaid PDL.[1]
- Oregon FFS Medicaid currently lists the CGRP antagonists Ajovy® (fremanezumab) and Emgality® (galcanezumab) as preferred agents for migraine prophylaxis with PA criteria (see **Appendix F**). This PA criteria was implemented on 11/1/2018 and last reviewed and edited by the Pharmacy and Therapeutics (P&T) committee in August 2020.[1]

Background:

Migraine headaches are a common ailment that affect approximately 16% of Americans.[2] These are divided into episodic migraines and chronic migraines. Episodic migraines are defined as experiencing zero to fourteen headache days per month; chronic migraines cause at least fifteen migraine days per month for more than three months consecutively.[2,3] Chronic migraines are much less common than episodic migraine and are estimated to affect 1-5% of Americans with migraines.[2] Migraine headaches appear to affect different patient populations at varying rates. Prevalence estimates by race from 2012 showed that migraines most affect Native Americans (17.7%), followed by Caucasians (14.3%), African Americans (14%), Hispanic Americans (12.9%), and least commonly Asian Americans (9.2%).[4] Migraines affect more women than men, with a sex prevalence ratio of 3:1.[2] By age, migraines affect mostly 18-44 year-old patients (17.9% prevalence), followed by 45-64 year-old patients (15.9%), and 65-74 year-old patients (7.3%).[5] Migraines affect more patients who earn less than $35,000 per year for family income (19.9% prevalence) than those earning greater than $35,000 per year (13.8%).[5] For patients younger than 65 years old, migraines affect 26% of Medicaid insured patients, which is much more than those covered by private insurance (15.1%).[5] Although estimates of migraine prevalence in Medicaid populations are known, estimates on abortive treatment utilization rates in this population are lacking in the medical literature and warrant investigation.

Migraines are treated acutely with abortive agents. Serotonin agonists (5-$HT_{1B, 1D}$), prescription only agents commonly referred to as "triptans", are the most commonly used abortive treatment.[3,6,7] However, there are many other abortive agents that can be obtained and utilized via prescription or over the counter, including acetaminophen and

nonsteroidal anti-inflammatory drugs (NSAIDs). For adult patients, the American Headache Society, the Canadian Headache Society, and the National Institute for Health and Care Excellence (NICE) guidelines recommend combination or monotherapy with the following medication classes for abortive treatment: triptans, NSAIDs, and acetaminophen containing products (e.g. Excedrin® [acetaminophen/aspirin/caffeine]).[3,6,7] Opioids (e.g. tramadol, codeine, and nasal butorphanol), ergot derivatives (e.g. dihydroergotamine), and butalbital containing products (e.g. Fioricet® [butalbital/acetaminophen/caffeine]) are generally *not* recommended by these guidelines for acute migraine treatment.[3,6,7] This is due to a lack of efficacy (for opioids and butalbital containing products) and increased safety risks (for opioids, ergot derivatives, and butalbital containing products).[3,6,7] For pediatric patients, the NICE guidelines give similar recommendations as they are intended for application in patients at least 12 years of age.[3] The American Academy of Neurology pediatric guidelines, which are endorsed by the American Academy of Pediatrics, recommend the use of ibuprofen, naproxen, or acetaminophen as first-line abortive agents.[8] If ineffective, triptans are reasonable second-line abortive therapy options.[8] Specifically, they recommend sumatriptan, zolmitriptan, rizatriptan, or almotriptan since these are the only triptans that have been Food and Drug Administration (FDA)-approved for use in pediatric patients.[8] Sumatriptan (when co-formulated with naproxen), zolmitriptan, and almotriptan are all FDA-approved for patients at least 12 years of age; rizatriptan is FDA-approved for patients 6 years and older.[9] Regardless of age, triptans are contraindicated for abortive treatment in patients with a past medical history of ischemic cardiovascular disease, cerebrovascular disease such as strokes, or uncontrolled hypertension as triptan use can increase the risk of potentiating these disease states.[9]

Since the publication of these guidelines, two CGRP antagonists (rimegepant and ubrogepant) have been FDA-approved for acute migraine treatment.[10,11] Some CGRP antagonists are approved exclusively for acute migraine treatment, while others are approved for prophylaxis (see **Table 2**). Lasmiditan, a serotonin ($5\text{-}HT_{1F}$) agonist, was also FDA-approved for acute migraine treatment in Oct 2019.[12]

Table 2: CGRP Antagonists and FDA Approved Uses[9]

Brand Name	Generic Name	FDA Approved Uses*
Nurtec®	Rimegepant	Migraine Treatment
Ubrelvy®	Ubrogepant	Migraine Treatment
Vyepti®	Eptinezumab	Migraine Prophylaxis
Aimovig®	Erenumab	Migraine Prophylaxis
Ajovy®	Fremanezumab	Migraine Prophylaxis
Emgality®	Galcanezumab	Migraine Prophylaxis Cluster Headache Prevention
*In adults only		

Medication overuse headaches (MOH) are a form of migraines or headaches that are caused by frequent utilization of abortive agents. Although the pathophysiology of MOH is not entirely clear, neuronal excitability in the cortical and trigeminal systems is known to increase after medication overuse and is strongly suspected to contribute to MOH.[13] All abortive agents have the potential for causing MOH, but to varying degrees.[6] Triptan use is generally limited to a maximum of 9 days per month to prevent the risk of MOH whereas acetaminophen and NSAIDs should be limited to a maximum of 14 days per month.[3,6] If patients are utilizing more than one medication class simultaneously, they should have at least 20 days per month free of abortive treatments in order to prevent MOH.[6]

Guidelines on when to initiate migraine prophylaxis vary slightly by professional society. For example, the American Family Physician guidelines recommend initiation of migraine prophylaxis in adult patients with at least 4 distinct migraines per month or at least 8 migraine days per month.[2] In contrast, the Canadian Headache Society guidelines recommend prophylaxis for adult patients with at least 3 moderate to severe migraines or at least 8 migraine days per month.[14] The NICE Guidelines recommend discussion of

the benefits and risks of prophylactic treatment for migraine with all patients 12 years old and over regardless of number of migraines per month by taking into account the patient's preferences, comorbidities, risk of adverse events and the impact of the headache on their quality of life.[3]

The American Academy of Neurology guidelines for pediatric migraine prevention, which is endorsed by the American Academy of Pediatrics, recommend discussion of the use of preventative therapies for patients with "frequent headaches or migraine-related disability or both."[15] Additionally, the pediatric guidelines also recommend emphasizing non-pharmacological interventions (such as trigger avoidance and encouraging good sleep hygiene) since the efficacy data for pharmacological interventions is less robust in pediatric patients.[15] In the majority of randomized controlled trials (RCTs) in pediatric patients, migraine prevention medications fail to demonstrate superiority to placebo. Broadly, placebo use alone led to a 50% or greater reduction in headache frequency in 30-61% of children.[15] Only three medications (topiramate, propranolol, and amitriptyline (when combined with cognitive behavioral therapy)) are recommended for migraine prevention in pediatric patients due to their slightly better evidence for efficacy as compared to placebo. For topiramate, a random effect model of 4 RCTs comparing topiramate to placebo led to a standardized mean difference (SMD) of 0.391 [95% confidence interval (CI) 0.127-0.655] in reducing the frequency of migraine days.[15] A SMD of 0.391 indicates that patient taking topiramate had on average 0.391 fewer days with migraines than patients taking placebo. A SMD of at least 0.2 is deemed clinically significant.[15] Propranolol use as compared to placebo in one RCT led to a risk ratio (RR) of 5.2 [95% CI 1.59-17] in leading to at least a 50% reduction in headache attacks.[15] Pediatric patients who receive amitriptyline plus cognitive behavioral therapy are more likely to have a reduction in headaches than those who receive amitriptyline alone (SMD 0.48 [95% CI 0.14-0.82]).[15]

All patients with chronic migraines (defined as at least fifteen migraine days per month for more than three months) qualify for preventative therapy regardless of which guidelines are referenced, and about 25-38% of patients with episodic migraines may also benefit from prophylaxis.[2,3,14,15] Of the patients who qualify for prophylaxis, the American Family Physician guidelines estimate that only about 3-13% of patients are prescribed a prophylactic agent.[2] This suggests that there is a gap in appropriate prophylactic agent use. Estimates of how many Medicaid patients with migraines are prescribed prophylactic agents are lacking and warrant investigation. **Table 3** lists the guideline recommended agents used to prevent migraines in adults who qualify for preventative therapy.

Table 3: Migraine Prophylaxis Agents Based on Highest Level of Evidence for Use in Adults[2,3,14-17]

Level of Evidence for Use	Medication Examples	
Level A Evidence – Established Efficacy (≥2 Class I studies)	Divalproex sodium Metoprolol tartrate Metoprolol succinate Propranolol	Sodium valproate (valproic acid) Timolol Topiramate
Level B Evidence – Probably Effective (1 Class I or 2 Class II studies)	Amitriptyline Atenolol	Nadolol Venlafaxine
Not Recommended – Established as possibly or probably ineffective	Clonazepam Feverfew Gabapentin Lamotrigine	Nabumetone Oxcarbazepine Telmisartan

Use of a migraine prophylactic agent reduces the utilization of abortive medications and other healthcare related costs (such as ED visits).[18] A retrospective study assessed healthcare resource utilization 6 months prior to and 12 months (broken into two 6-month time frames) after the initiation of a preventative agent. Patients with migraines used a mean of 7.1 units of sumatriptan per month prior to being prescribed a preventative agent. This decreased to 6.6 units per month in the first 6 months after preventative therapy initiation and decreased further to 5.6 units per month in the second 6 months (a decrease of 21.1%, P= 0.0004).[18] Comparing the 6 months prior to preventative therapy and the second 6 month segment after preventative agent initiation, office and other outpatient visits for migraines reduced by 51.1%. ED visits for migraines were

reduced by 81.8%.[18] Thus, appropriately using preventative therapies for migraines has the potential to significantly reduce healthcare costs associated with utilization of abortive therapies, outpatient visits, and ED visits.

The purpose of this drug use evaluation is to determine what percentage of the Oregon FFS Medicaid population is currently utilizing triptans chronically, how many of those patients are also utilizing a migraine preventative therapy, and if there is a gap in treatment for preventative therapy use. Additionally, an analysis of CGRP antagonist use since PA implementation was conducted to assess CGRP utilization and evaluate if current PA criteria is overly burdensome.

Methods:

This descriptive and retrospective analysis included all Oregon FFS Medicaid patients (all ages) who had been prescribed any FDA-approved triptan chronically (defined below). Other abortive agents, such as NSAIDs, were excluded since they can readily be obtained over the counter and the data would be less reliable. Additionally, claims data from 2020 was excluded due to the anticipated confounders as a result of the COVID-19 pandemic. High stress levels are a common trigger for migraines,[2] and thus patients may have utilized triptans more frequently during 2020. Additionally, changes in insurance status and ability to access healthcare services for conditions such as migraines were likely fundamentally altered from a "typical" year.

Chronic use of triptans was defined as any three FFS claims within a 120-day period to indicate fills of triptan for three consecutive months. A 4-month window was chosen to allow for gaps between refills. The index date was defined as the date of the first claim for the first triptan within the 120-day window. Patients with 3 claims for *any* triptan were included to allow for switching between different agents. Additionally, all patients with at least 1 triptan claim during this time frame were queried for a medical claim with a diagnosis of migraine (see **Appendix B** for a list of included ICD-10 codes) to better describe what the triptan and prophylaxis agent (if any) was being utilized for. Patients on chronic triptans were evaluated for prophylactic medication use. Any claim for one of the prophylactic agents with level A or B evidence from **Table 3** (HSN and GSN codes included in **Appendix C**) during the time frame of April 1, 2018 through Dec 31, 2019 (6 months prior to 3 months after the chronic triptan use time frame) was evaluated.

Patients identified as having a claim for a prophylaxis agent ("prophylaxis users") were assessed for the presence of an adequate prophylaxis trial. Guidelines recommend that all prophylactic agents be tried for at least 2 consecutive months to determine their efficacy at reducing migraine severity and/or frequency. An adequate trial was defined as having at least two claims of the same prophylactic medication in consecutive months. A 14-day gap in therapy between fills was allowed to account for imperfect refill timing. The average number of claims for triptans per month was compared between chronic triptan users who did and did not have a co-prescribed prophylactic agent. Additionally, the number of unique patients with ED visits and hospitalizations for migraines (utilizing the same ICD-10 codes listed in **Appendix B**) was compared between chronic triptan users who did and did not have a co-prescribed prophylaxis agent. However, prophylaxis users may interact with the healthcare system more in general than non-prophylaxis users, potentially introducing a confounding variable. In order to assess baseline rates of ED visits and hospitalizations for prophylaxis and non-prophylaxis users, unique patient ED visits and hospitalizations for *any* diagnosis was also gathered. We also compared patients who did and did not have an adequate trial of a prophylactic medication.

To describe overall utilization of the CGRP antagonists over time, we included the number of unique prior authorizations (both approved and denied) for all FDA-approved CGRP antagonists (see **Table 2**) from Nov 1, 2018 through Dec 31, 2020. We identified unique PAs via unique PA numbers. All unique prescriptions for a CGRP antagonist medication from Nov 1, 2018 through Dec 31, 2020 with error codes listed in **Appendix D** and without error codes listed in **Appendix E** were included in the analysis. Error codes in **Appendix E** would indicate these claims were denied for procedural reasons. The identified claims were then assessed for the most common reasons for denial using a descriptive analysis.

Results:

From Oct 1, 2018 through Sept 30, 2019, an average of 113,228 patients were enrolled in Oregon Medicaid FFS for the entire year (9,436 enrolled patients per month). Of those patients, 1,178 (1% of the entire Oregon FFS Medicaid population) had at least one triptan claim during the same time frame. Of the 1,178 triptan users, only 169 patients (14% of all triptan users) met the definition of a "chronic triptan user" (3 FFS claims for triptans in a continuous 120-day period). Demographics for patients with at least one triptan claim and chronic triptan users is listed in **Table 4**. There are no obvious differences between all triptan users and chronic triptan users. However, chronic triptan users included slightly more female patients (88% vs. 83%). Of note, only 66% of all triptan users and 62% of chronic triptan users had a migraine diagnosis. The majority of chronic triptan users were 18-44 years old (63%); however, 6% of chronic triptan users were 0-17 years old.

Table 4: Demographic Data for All Triptan Users and Chronic Triptan Users in the Oregon Medicaid FFS Population:

Demographic Parameter	All Triptan User (N = 1178) Number of patients (% of *all* triptan users)	Chronic Triptan User (N=169) Number of patients (% of *chronic* triptan users)
Average Age (years)	35 (range 5-64)	38 (range 10-63)
0-17 years	149 (13%)	10 (6%)
18-44 years	733 (62%)	107 (63%)
45-64 years	296 (25%)	52 (31%)
65+ years	0 (0%)	0 (0%)
Sex		
Female	978 (83%)	149 (88%)
Race		
White	511 (43%)	89 (53%)
Black	17 (1%)	0 (0%)
Other	172 (15%)	30 (18%)
Unknown	478 (41%)	50 (30%)
Patients with Migraine Diagnosis	772 (66%)	105 (62%)
Number of months/year triptan filled		
10-12	6 (1%)	6 (4%)
7-9	24 (2%)	24 (14%)
4-6	70 (6%)	63 (37%)
1-3	1078 (92%)	76 (45%)

Of the 169 chronic triptan users, 92 (54%) also had a claim for one or more guideline recommended prophylactic agents (see **Table 5**). Of the 92 patients with prescriptions for prophylaxis medications, 78 (85%) had an adequate trial of an agent (see **Table 6**). All three medication classes were utilized roughly equally with 47% of patients prescribed an anticonvulsant, 46% a beta-blocker, and 36% an antidepressant. The most commonly prescribed prophylaxis medications are topiramate (40%), propranolol (30%), and amitriptyline (23%). The majority of the prescribed prophylaxis agents have Level A evidence for their use (60%).

Table 5: Type of Prophylaxis Agent (N=92)

	Number of patients (percent of those prescribed ***any*** prophylaxis agent use)*
Breakdown by specific generic medication:	
Anticonvulsants • Topiramate • Divalproex • Valproate or Valproic Acid	43 (47%) 37 (40%) 5 (5%) 1 (1%)
Beta-blockers • Propranolol • Metoprolol (tartrate or succinate) • Atenolol • Timolol • Nadolol	42 (46%) 28 (30%) 10 (11%) 4 (4%) 0 (0%) 0 (0%)
Antidepressants • Amitriptyline • Venlafaxine	33 (36%) 21 (23%) 14 (15%)
Breakdown by level of evidence**	
Prescribed a Level A agent only	55 (60%)
Prescribed a Level B agent only	20 (22%)
Prescribed both a Level A and Level B agent†	17 (18%)
*Medications and classes are not mutually exclusive as patients may have been prescribed more than one prophylaxis agent **see **Table 3** for a list of medications by evidence for use level †this includes concurrent or consecutive use	

Table 6: Patients with the same prophylactic agent for at least 2 consecutive months (N=78)

	Number of patients (percent of those on ***prophylaxis agent for at least 2 months***)*
Breakdown by specific generic medication:	
Anticonvulsants • Topiramate • Divalproex • Valproate or Valproic Acid	32 (41%) 29 (37%) 3 (4%) 0 (0%)
Beta-blockers • Propranolol	36 (46%) 23 (29%)

• Metoprolol (tartrate or succinate) • Atenolol • Timolol • Nadolol	9 (12%) 4 (5%) 0 (0%) 0 (0%)
Antidepressants • Amitriptyline • Venlafaxine	24 (31%) 16 (21%) 9 (12%)
Breakdown by level of evidence**	
Prescribed a Level A agent only	49 (63%)
Prescribed a Level B agent only	18 (23%)
Prescribed both a Level A and Level B agent†	10 (13%)
* Medications and classes are not mutually exclusive as patients may have been prescribed more than one prophylaxis agent **see **Table 3** for a list of medications by evidence for use level †this includes concurrent or consecutive use	

When comparing chronic triptan users who had any prophylaxis use versus no prophylaxis use, the average number of triptans dispensed/year is slightly lower (6.8 claims per year versus 7.1 claims per year, respectively). Patients with any prophylaxis use had more ED visits for any diagnosis (39 unique patients with ED visits for any diagnosis) as compared to non-prophylaxis user (25 patients) (see **Table 7**). Prophylaxis users and non-prophylaxis users had similar numbers of unique patients who had ED visits specifically for migraines. There was also no difference between adequate prophylaxis trial users and general prophylaxis use (see **Table 7**). However, numbers of hospitalizations and ED visits is low overall.

Table 7: Clinical Outcomes Associated with No Prophylaxis Use, Any Prophylaxis Use, and Adequate Trial Prophylaxis Use:

	Number of patients (% of ***chronic triptan users***)	Average number of triptan claims per year	Number of unique patients with ED visits for ***any*** diagnosis	Number of unique patients with ED visits for ***migraines***	Number of unique patients with hospitalizations for ***any*** diagnosis	Number of unique patients with hospitalizations for ***migraines***
No prophylaxis use	77 (46%)	7.1	25 (33% of NON-prophylaxis users)	3 (4% of NON-prophylaxis users)	4 (5% of NON-prophylaxis users)	0 (0%)
Any prophylaxis use	92 (54%)	6.8	39 (42% of prophylaxis users)	5 (5% of prophylaxis users)	7 (8% of prophylaxis users)	0 (0%)
Adequate trial use*	78 (46%)	6.7	32 (41% of adequate trial users)	4 (5% of adequate trial users)	4 (5% of adequate trial users)	0 (0%)
*Adequate trial defined as the same prophylactic agent dispensed for at least 2 consecutive months						

Since the PA criteria for CGRP antagonists was implemented, 579 unique paid and denied prescriptions for all CGRP antagonists were identified, regardless of indication. Of those 579 prescriptions, 525 (91%) are for agents specifically FDA-approved for migraine prophylaxis. For the migraine prophylaxis agents, 51% (N= 268) of the prescriptions

were denied. Since these data reflect a two-year time period and CGRP antagonists are indicated for chronic use, these values may reflect multiple prescription (Rx) numbers per patient. See **Tables 8 and 9** for a full analysis of paid and denied prescriptions for all CGRP antagonists and only those indicated for prophylaxis respectively.

During the same time frame of two years, 205 unique PAs were submitted for review for all CGRP antagonists. Of those 205 PAs, 180 (88%) were for prophylaxis agents. Of the 180 unique PAs submitted for prophylaxis agents, 71% were approved. This data was not delineated by initial PA approval versus renewal requests. Because the initial PA approval is valid for up to 3 months and the renewal approval is valid for up to 6 months, the data on unique PAs may represent multiple PA requests for individual patients. See **Tables 10 and 11** for a full analysis for approved and denied PAs for all CGRP antagonists and only those indicated for prophylaxis.

Table 8: Total Prescriptions for all CGRP Antagonists

Number of Unique Prescriptions for ***all*** CGRP Antagonists	Number of Rxs (% of total)
Total	579
Paid	274 (47%)
Denied	305 (53%)

Table 9: Total Prescriptions for Prophylaxis CGRP Antagonists

Number of Unique Prescriptions for ***prophylaxis-only*** CGRP Antagonists	Number of Rxs (% of total)
Total	525
Paid	257 (49%)
Denied	268 (51%)

Table 10: Total PAs for All CGRP Antagonists

Unique PAs for ***all*** CGRP Antagonists	Number of PAs (% of total)
Total	205
Approved PAs	141 (69%)
Denied PAs	64 (31%)

Table 11: Total PAs for Prophylaxis CGRP Antagonists

Unique PAs for ***prophylaxis-only*** CGRP Antagonists	Number of PAs (% of total)
Total	180
Approved PAs	127 (71%)
Denied PAs	53 (29%)

For CGRP antagonists indicated for migraine prophylaxis, the most common reason a claim was denied was for prior authorization (N = 253, 94%) (see **Table 12**). However, only a total of 180 PAs were requested (see **Table 11**). What portion of these denied claims, if any, that would have met PA criteria if they had requested one is unknown. However, the majority of PAs that were requested were approved (N = 127, 71%) (see **Table 11**).

For PA denials of CGRP antagonists indicated for migraine prophylaxis, the most common reason a PA was denied is that the request was determined not to be medically appropriate (did not meet PA approval criteria as outlined in **Appendix F**) with 94% of PAs being denied for this reason (see **Table 13**).

Table 12: Reasons for Prescription Denial for Prophylaxis-only CGRP Antagonists

Reason for ***prescription*** denial for prophylaxis-only CGRP Antagonists	Number of Rxs (% of *denied* Rxs)
Total denied claims	268
NDC Requires PA	253 (94%)
Claim failed a ProDUR Alert	19 (7%)
Claim denied for ProDUR Reasons	9 (3%)
Day supply limit exceeded for covered NDC	5 (2%)
Prescribing physicians ID not on file	3 (1%)
Units exceed Authorized units on PA master file	2 (1%)

Table 13: Reasons for PA Denial for Prophylaxis-Only CGRP Antagonists

Reason for ***PA*** denial for prophylaxis-only CGRP Antagonists	Number of Rxs (% of *denied* PAs)
Total denied PAs	53
Request was determined not medically appropriate	50 (94%)
Treatment of condition is not a covered service on OHP	2 (4%)
Drug requested is not covered by benefit package	1 (2%)

Discussion:

From Oct 1, 2018 through Sept 20, 2019, only a small percentage (1%) of Oregon FFS Medicaid patients had at least one triptan claim (1,178 patients). Even fewer were chronic triptan users (N = 169). This is much lower than the estimated 26% prevalence of Medicaid patients with migraines,[5] which may suggest that the Oregon FFS Medicaid population has a lower prevalence of patients with migraines, that patients are utilizing non-triptan therapies (such as acetaminophen or NSAIDs) more often, or that patients are not staying enrolled in FFS long enough to accurately identify patients with migraines based on claims data alone (because they switch to a coordinated care organization (CCO)). The majority of chronic triptan users were female and between the ages of 18 and 44 years old, which matches the expected demographics of patients with migraines based on epidemiological data.[5] However, there were also patients less than 18 years old who used triptans (n=149), and a small number of pediatric patients were on chronic therapy (n=10).

Based on guideline recommendations, all patients who meet the definition of chronic triptan use would qualify for prophylaxis treatment. However, only about half of chronic triptan users were prescribed a guideline recommended prophylaxis agent. This is still higher than rates reported in the literature. For patients with *episodic* migraines, prophylaxis use is estimated at 3-13% of patients (when approximately 38% would likely benefit).[2] A separate survey study looking at all migraines (both *episodic* and *chronic*) found that only 13% of patients were using a prophylaxis agent.[19] In that same study, 43% of patients had never used a prophylaxis agent before, but 32% of that 43% would qualify for prophylaxis use.[19] If a prophylaxis agent was initiated, the majority of patients had at least 2 consecutive months of claims for that agent, which follows guideline recommendations of at least 8 weeks of prophylactic therapy to determine efficacy. This appears to indicate that initiation of treatment (not continuation of therapy) is the primary barrier to appropriate prophylaxis use. However, 2 consecutive months of claims may not necessarily indicated 2 months of medication adherence. If patients were initiated on prophylaxis therapy, there does not appear to be one class of medications favored over others. All three major medication classes were utilized roughly equivalently. This is consistent with guidelines which do not recommend one specific prophylaxis agent over another, and instead recommend that patient specific factors and comorbidities should be taken into account when choosing an appropriate agent. Regardless of the specific medication being utilized, the majority of patients were prescribed medications with Level A evidence.

Because there are so few chronic triptan users (N = 169) and even fewer who were also prescribed a prophylaxis agent (N = 92), determining the impact prophylaxis therapy has on triptan utilization, ED visits, and hospitalizations is difficult. However, prophylaxis users do appear to use slightly less triptans (6.8 claims per year versus 7.1 claims per year for non-prophylaxis users). Decreased triptan utilization implies less migraine days per month (a marker of prophylaxis agent efficacy). Prophylaxis agents may also decrease migraine severity, which unfortunately cannot be assessed by claims data, but would certainly improve quality of life even if the number of migraine days per month remains the same for patients. Very few patients (prophylaxis users and non-users alike) sought ED care for migraines. However, more prophylaxis users sought ED care for ALL diagnoses as

compared to non-prophylaxis users. This may imply that non-prophylaxis users are generally less engaged with the healthcare system as a whole and may not have sought ED care for their migraines even if their migraine warranted ED levels of care. This less healthcare engagement in general may potentially be masking the true impact prophylaxis use has on ED utilization. Prophylaxis users having more ED visits may also suggest that those on prophylactic medications have more severe disease. There were no hospitalizations for migraine related diagnoses identified, which is expected as migraines do not typically require inpatient level of care.

Since Oregon FFS Medicaid implemented its PA criteria for CGRP antagonists on Nov 1, 2018 to Dec 31, 2020, about half of prescriptions were denied. If a PA was requested for the prophylaxis CGRPs, the majority of them were approved (71%). For many patients, a PA was not requested and it is unclear what portion of these patients may have met PA criteria. For the denied PAs, the most common reason for denial is that the request is not medically appropriate (i.e. does not meet PA criteria). Interestingly, 2 PAs were denied for the reason of "treatment of condition is not a covered service on OHP," suggesting that these specific PAs were requesting to use prophylaxis-only CGRP antagonists off-label but for what indication is unclear. Alternatively, these 2 PAs could indicate that those patients didn't have a drug benefit altogether (and may have only had emergency service coverage through FFS Medicaid, not medication coverage).

Overall, relatively few CGRP antagonists indicated for migraine prophylaxis were prescribed with a total prescription count over a two year period of 525; even fewer were successfully paid (N=257). Since a high proportion of requested PAs were approved, this indicates that the PA criteria is consistent with prescriber practice. This may also suggest that providers are only requesting the PA if they have determined their patient meets criteria (as most clinicians may not request PA approval if they know that their patient does not meet criteria). However, there is no way to determine if the un-requested PAs would or would not have met criteria.

Limitations:

The main limitation of this analysis is that there is no guaranteed way to ensure that the agents assessed for migraine prophylaxis in research question 2 are indeed being used for migraine prophylaxis since all of these agents have other indications as well. For example, the anticonvulsants may be used for epilepsy and not necessarily migraine prophylaxis. The beta-blockers may be used for heart failure or post-myocardial infarction care rather than migraine prophylaxis. The antidepressants may be used for anxiety or depression rather than migraine prophylaxis. However, this limitation was mitigated as much as possible by only including first and second-line guideline recommended prophylaxis agents with the most efficacy data, and thus would theoretically be prescribed most often. Additionally, this limitation was mitigated by only assessing patients for prophylaxis use in chronic triptan users. Furthermore, guidelines recommend that patient factors (such as co-morbidities) be taken into account when selecting a prophylaxis agent anyway and would recommend that a patient with depression should be started on an antidepressant in order to treat both the depression and the migraines with one medication for example. Thus, it is likely safe to assume that the majority (if not all) of the data reported for research question 2 is likely to reflect agents prescribed for migraine prophylaxis, though they may treat another indication simultaneously.

Another limitation of this analysis is that it did not assess non-triptan abortive therapy use (such as NSAIDs or acetaminophen) since these agents can be obtained over the counter and their use would have been difficult to identify. This may lead to an under-representation of migraine sufferers in the Oregon FFS Medicaid population who may or may not be utilizing triptans for their abortive treatment.

For patients prescribed triptans, there may also be a gap in true representation of triptan utilization if patients paid cash for the triptan (rather than using their Oregon FFS Medicaid benefits). The primary reason a patient may pay cash rather than using insurance is to by-pass the quantity limits imposed by the PDL. If patients are doing this, the analysis would not be able to capture these prescriptions since claims information was used to gather data. Additionally, using claims data alone to identify chronic triptan users may inherently leave out patients due to the nature of Medicaid patients entering and exiting Oregon FFS Medicaid over time by joining and leaving coordinated care organizations (CCOs). Theoretically, there may be more chronic triptan users in the whole Oregon Medicaid population but because those patients were using CCO benefits (and not FFS) we would not have been able to capture these patients with this data analysis.

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Appendix A: Oregon FFS Medicaid Quantity Limits for Preferred and Non-preferred Triptans

Oregon FFS Medicaid Status	Generic Name	Formulation	Brand Name	Quantity Limit per Month
Preferred (Y)	Naratriptan	Tablets	Amerge	9 tabs
Preferred (Y)	Sumatriptan	Tablets	Imitrex & generics	9 tabs
Preferred (Y)	Sumatriptan	Nasal Spray	Imitrex & generics	18 spray units
Preferred (Y)	Sumatriptan	Injectable	Imitrex & generics	6 vials
Preferred (Y)	Zolmitriptan	Tablets	Zomig Zomig ZMT	6 tabs
Preferred (Y)	Zolmitriptan	Nasal spray	Zomig NS	3 packages (18 spray units)
Non-preferred (N)	Almotriptan	Tablets	Axert	12 tabs
Non-preferred (N)	Eletriptan	Tablets	Relpax	6 tabs
Non-preferred (N)	Frovatriptan	Tablets	Frova	9 tabs
Non-preferred (N)	Rizatriptan	Tablets	Maxalt Maxalt MLT	12 tabs
Non-preferred (N)	Sumatriptan	Nasal powder	Onzetra Xsail	6 nosepieces
Non-preferred (N)	Sumatriptan	Injectable	Sumavel	6 jet injectors
Non-preferred (N)	Sumatriptan	Injectable	Zembrace Symtouch	12 auto-injectors
Non-preferred (N)	Sumatriptan/naproxen	Tablets	Treximet	9 tabs

Appendix B: ICD-10 Codes of Interest for Migraine Diagnoses

ICD-10 Code	Meaning of ICD-10 Code
G43.001	Migraine without aura, not intractable, with and without status migrainosus
G43.009	
G43.011	Migraine without aura, intractable, with and without status migrainosus
G43.019	
G43.101	Migraine with aura, not intractable, with and without status migrainosus
G43.109	
G43.111	Migraine with aura, intractable, with and without status migrainosus
G43.119	
G43.401	Hemiplegic migraine, not intractable, with and without status migrainosus
G43.409	
G43.411	Hemiplegic migraine, intractable, with and without status migrainosus
G43.419	
G43.501	

G43.509	Persistent migraine aura without cerebral infarction, not intractable, with and without status migrainosus
G43.511	Persistent migraine aura without cerebral infarction, intractable, with and without status migrainosus
G43.519	
G43.601	Persistent migraine aura with cerebral infarction, not intractable, with and without status migrainosus
G43.609	
G43.611	Persistent migraine aura with cerebral infarction, intractable, with and without status migrainosus
G43.619	
G43.701	Chronic migraine without aura, not intractable, with and without status migrainosus
G43.709	
G43.711	Chronic migraine without aura, intractable, with and without status migrainosus
G43.719	
G43.A0	Cyclical vomiting in migraine not intractable and intractable
G43.A1	
G43.B0	Ophthalmoplegic migraine not intractable and intractable
G43.B1	
G43.C0	Periodic headache syndromes in child or adult not intractable and intractable
G43.C1	
G43.D0	Abdominal migraine not intractable and intractable
G43.D1	
G43.801	Other migraine, not intractable, with and without status migrainosus
G43.809	
G43.811	Other migraine, intractable, with and without status migrainosus
G43.819	
G43.821	Menstrual migraine, not intractable, with and without status migrainosus
G43.829	
G43.831	Menstrual migraine, intractable, with and without status migrainosus
G43.839	
G43.901	Migraine, unspecified, not intractable, with and without status migrainosus
G43.909	
G43.911	Migraine, unspecified, intractable, with and without status migrainosus
G43.919	

Appendix C: Guideline Recommended Migraine Prophylaxis Agents with Highest Level of Evidence for Use and their associated HSN and GSN codes:

Level of Evidence for Use	Medication Examples	HSN	GSN
Level A Evidence – Established Efficacy (≥2 Class I studies)	Topiramate	011060	064519 (exclude this GSN)
	Propranolol	002101	043103, 015995 (exclude these GSNs)
	Metoprolol (tartrate and succinate)	002102, 006323	005129, 019808, 025856, 023600 (exclude these GSNs)
	Timolol	002105	005140, 005141, 005142 (include *only* these GSNs)
	Divalproex sodium	001884	All
	Sodium valproate (valproic acid)	001882, 001883	051616, 031533 (exclude these GSNs)
Level B Evidence – Probably Effective (1 Class I or 2 Class II studies)	Amitriptyline	001643	023199 (exclude this GSN)
	Venlafaxine	008847	All
	Atenolol	002104	023195 (exclude this GSN)
	Nadolol	002103	023603 (exclude this GSN)

Appendix D: Error Codes INCLUDED in the Analysis of Denied CGRP Antagonist Claims and PAs:

Error Code	Error Code Description
3002	NDC Requires PA
7002	Claim denied for Pro-DUR reasons
7000	Claim failed a Pro-DUR alert
1026	Prescribing physician ID Not on file
4026	Day supply limit exceeded for covered NDC
3000	Units exceed authorized units on PA master file

Appendix E: Error Codes EXCLUDED in the Analysis of Denied CGRP Antagonist Claims and PAs:

Error Code	Error Code Description
2017	Recipient services covered by HMO Plan
2508	Recipient covered by private insurance
576	Claim has third-party payment
4999	This drug is covered by Medicare Part D
4002	Non-covered drug
2002	Recipient not eligible for header date of service
4890	Non covered drug class
4891	Not covered drug class
643	Invalid other coverage code
4007	Non-covered NDC due to CMS termination
628	Other coverage reject code required for OCC 3
2507	Recipient has more than one insurance carrier

Calcitonin Gene-Related Peptide (CGRP) antagonists

Goal(s):
- Promote safe use of CGRP inhibitors in adult patients
- Promote use that is consistent with medical evidence and product labeling for migraine prevention, acute migraine treatment and cluster headache prevention (Table 1).

Length of Authorization:
- Initial: Up to 3 months
- Renewal: Up to 6 months

Requires PA:
- All calcitonin gene-related peptide (CGRP) antagonists (eptinezumab, erenumab, fremanezumab, galcanezumab, rimegepant and ubrogepant) pharmacy and physician administered claims

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

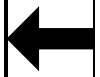
Table 1. FDA Approved Indications for CGRP antagonists

Drug	FDA Approved Indication
Eptinezumab	Preventative migraine treatment
Erenumab	Preventative migraine treatment
Fremanezumab	Preventative migraine treatment
Galcanezumab	Preventative migraine treatment and cluster headache prevention
Rimegepant sulfate	Acute migraine treatment
Ubrogepant	Acute migraine treatment

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA-approved indication (Table 1)?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness

3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Is this a request for renewal of a previously approved Fee-For-Service prior authorization of a CGRP antagonist for management of migraine headache?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #5
5. Is the medication being prescribed by or in consultation with a neurologist or headache specialist?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Do chart notes indicate headaches are due to medication overuse?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to # 7
7. Is the request for acute migraine treatment AND the patient is an adult (18 years or older)?	**Yes:** Go to #12	**No:** Go to #8
8. Is the request for the prevention of cluster headache AND the patient is an adult (18 years or older)?	**Yes:** Go to #15	**No:** Go to #9
9. Is there documentation that the patient has experienced 4 or more migraine days in the previous month AND the patient is an adult (18 years or older)?	**Yes:** Document migraine days per month _____ Go to # 10	**No:** Pass to RPh. Deny; medical appropriateness

Specific to Rimegepant (Nurtec) and Ubrogepant (Ubrelvy), which are indicated for acute treatment



Specific to Galcanezumab (Emgality), which is indicated for both migraine and cluster headache prevention

10. Has the patient failed an adequate trial (≥6 weeks with a documented adherence of ≥80%) of an FDA-approved migraine prophylaxis medication from each of the following classes: beta-blockers, anticonvulsants, and tricyclic antidepressants? OR Does the patient have a documented intolerance, FDA-labeled contraindication, or hypersensitivity to each of the above migraine prophylaxis classes?	**Yes:** Document agents used and dates _____ _____ Go to # 11	**No:** Pass to RPh. Deny; medical appropriateness
11. Has the patient received an injection with botulinum toxin for headache treatment once in the previous 2 months?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for up to 3 months
12. Has the patient failed adequate trials (3 or more different triptans) or have contraindications to triptans?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness. Recommend triptan trial.
13. Does the patient have chronic migraines?	**Yes**: Go to #14	**No**: Approve for 3 months
14. Does the patient have a history of at least 4 migraines a month AND is on preventative migraine therapy (excluding other CGRP inhibitors)?	**Yes:** Approve for up to 3 months	**No:** Pass to RPh. Deny; medical appropriateness

15. Does the patient have at least 4 headache attacks per week AND have a history of cluster headaches beyond one month?	**Yes:** Go to #16	**No:** Pass to RPh. Deny; medical appropriateness
16. Has the patient failed at least 2 cluster headache preventative treatments (i.e., lithium, verapamil, melatonin, frovatriptan, prednisone, subocciptal steroid injection, topiramate, and valproate)?	**Yes**: Approve for up to 3 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Do chart notes indicate headaches are due to medication overuse?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #2
2. Is the renewal request for acute migraine treatment?	**Yes:** Go to #5	**No:** Go to #3
3. Is the renewal request for migraine prevention?	**Yes:** Go to #4	**No:** Go to # 6
4. Has the patient experienced a documented positive response to therapy, as demonstrated by a reduction in migraine headache frequency and/or intensity from baseline?	**Yes:** Document response Approve for up to 6 months (e.g. minimum 2 doses for treatment given every 3 months)	**No:** Pass to RPh. Deny; medical Appropriateness
5. Has the patient demonstrated a response to therapy as indicated by a reduction in headache frequency and/or intensity?	**Yes:** Document response Approve for up to 6 months	**No:** Pass to RPh. Deny; medical Appropriateness
6. Is the renewal request for cluster headache prevention?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical Appropriateness

7. Does the patient have documentation of a reduction of at least 8 cluster headaches per month?	**Yes:** Document response Approve for up to 6 months	**No:** Pass to RPh. Deny; medical Appropriateness

P&T/DUR Review: 8/20 (KS); 5/19; 9/18 (DE)
Implementation: 11/1/2018

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Prior Authorization Criteria Update: Cystic Fibrosis

Purpose of Update:

The purpose of this prior authorization (PA) update is to review current criteria for the use of lumacaftor/ivacaftor (LUM/IVA) (Orkambi®) in pediatric patients. The combination of LUM/IVA was approved after phase 3 trials demonstrated its efficacy for the management of cystic fibrosis (CF) in patients 12 years of age and older who were homozygous for the F508del mutation in the CFTR gene.[1] It is currently FDA-approved for those age 2 years and older who are homozygous for the F508del mutation in the CFTR gene.[2] This patient group includes approximately 34% of the United States CF population.[3] 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_1 (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). [1]

Initial PA criteria included a manual review and assessment of clinical severity of disease from the medical director for all patients younger than 12 years of age prescribed LUM/IVA. This decision was based on 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 an open-label study resulting in no significant changes in percent predicted forced expiratory volume (ppFEV1).[4] Additionally, a total of 11 patients (19.3%) had elevations in liver transaminases more than 3-times the upper-limit-of-normal (ULN) and 5 patients (8.8%) had elevations more than 5-times ULN.[4] Another phase 3 study evaluating nonclinical outcomes demonstrated a decrease in lung clearance index, which indicates an improvement in lung ventilation, with LUM/IVA compared to placebo. [5]

Approval for patients 2 to 5 years of age was based on a 24-week, phase 3, non-randomized open-label trial in 60 patients.[6] This study was designed as a safety and pharmacokinetic study and funded by Vertex Pharmaceuticals. FDA approved the expanded indication based on the study results that demonstrated treatment with the drug for 24 weeks was generally safe and well tolerated, with a safety profile similar to patients aged 6 years of age and older. The most common adverse event was cough (63%). Three patients discontinued treatment due to elevated liver enzymes. During the 24 weeks, 9 (15%) of the patients had elevated liver transaminases more than 3-times ULN. [6] An ongoing extension study is underway to assess longer-term safety and durability of the beneficial effects of lumacaftor and ivacaftor in this age group.

Recommendation:

- Remove manual review by medical director for consistent with FDA labeling and standard of care from PA criteria for use of LUM/IVA in patients less than 12 years of age (**Appendix 1**).
- Add a link to FDA labeling in the PA criteria to ensure all approved CFTR mutations are current.

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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
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1: Approved and Funded Indications for Oral Cystic Fibrosis Modulators

Drug Name	FDA approved CFTR mutation	Age
Ivacaftor (Kalydeco)	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 or a mutation in the CFTR gene that is responsive based on in vitro	4 months to < 6 months AND ≥ 5 kg ≥ 6 months

	data. See drug labeling for a comprehensive list of approved mutations: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=203188	
Lumacaftor/ivacaftor (Orkambi)	Homozygous Phe508del	≥ 2 years
Tezacaftor/Ivacaftor (Symdeko)	Homozygous Phe508del, 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 or a mutation in the CFTR gene that is responsive based on in vitro data. See drug labeling for a comprehensive list of approved mutations: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=210491	≥ 6 years
Elexacaftor/tezacaftor/ivacaftor (Trikafta)	At least one Phe508del mutation (homozygous or heterozygous) or a mutation in the CFTR gene that is responsive based on in vitro data. See drug labeling for a comprehensive list of mutations: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=212273	≥ 12 years

Approval Criteria		
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)?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #2

Approval Criteria		
2. Does the patient have a diagnosis of Cystic Fibrosis?	**Yes:** Record ICD10 code. Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the request from a practitioner at an accredited Cystic Fibrosis Center or a pulmonologist?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the request for an FDA approved age and CFTR gene mutation as defined in Table 1?	**Yes:** Go to #5	**No:** 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?	**Yes:** Go to #7	**No:** Go to #8

Approval Criteria		
7. Does the patient have a documented R117H mutation in the CFTR gene detected by a CF mutation test?	**Yes:** Pass to RPh. Refer request to Medical Director for manual review and assessment of clinical severity of disease for approval.	**No:** Go to #810 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?~~	~~**Yes:** Go to #9~~	~~**No:** Go to #10~~
~~9. Is the patient younger than 12 years of age?~~	~~**Yes:** Refer case to OHP Medical Director for manual review and assessment of clinical severity of disease~~	~~**No:** Go to #10~~
~~10.~~8. 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? • Dornase alfa; AND • Hypertonic saline; AND • Inhaled or oral antibiotics (if appropriate)?	**Yes:** Go to #911	**No:** Pass to RPh. Deny; medical appropriateness
~~11.~~9. Is the patient on concomitant therapy with a strong CYP3A4 inducer (see Table 1)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #102

Approval Criteria		
~~12.~~10. What are the baseline liver function (AST/ALT) and bilirubin levels (within previous 3 months)?	Document labs. Go to #1~~13~~ If unknown, these labs need to be collected prior to approval.	
~~13.~~11. Is medication dosed appropriately based on age, weight, and co-administered drugs (see dosing and administration below)?	**Yes:** Approve for 6 months. If approved, a referral will be made to case management by the Oregon Health Authority.	**No:** 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?	**Yes:** Go to #2	**No:** Pass to RPh; Deny (medical appropriateness)

Renewal Criteria		
2. Does the patient have documented response to therapy as defined as below : For patients age ≥6 years: • An improvement or lack of decline in lung function as measured by the FEV1 when the patient is clinically stable; OR • A reduction in the incidence of pulmonary exacerbations; OR • A significant improvement in BMI by 10% from baseline? For patients age 2-5 years (cannot complete lung function tests) • Significant improvement in BMI by 10% from baseline; OR • Improvement in exacerbation frequency or severity	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Have liver function tests been appropriately monitored? What are the most recent liver function tests (AST, ALT, and bilirubin)? Note: Monitoring LFTs is recommended every 3 months for the first year, followed by once a year.	Document. Go to #4 Note: Therapy should be interrupted in patients with AST or ALT >5x the upper limit of normal (ULN), or ALT or AST >3x ULN with bilirubin >2x ULN.	
4. Is the CFTR modulator dosed appropriately based on age, weight, and co-administered drugs (see dosing and administration below)?	**Yes:** Approve for additional 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Dosage and Administration:

<u>Ivacaftor:</u>

- Adults and pediatrics age ≥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
- ≥ 14 kg: 75 mg packet every 12 hours

- Hepatic Impairment
  - Moderate Impairment (Child-Pugh class B):
    - Age ≥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 ≥ 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 **twice weekly** (one-seventh of normal initial dose)
Fluconazole Erythromycin Clofazimine	CYP3A4 moderate inhibitors	Reduce IVA dose to 1 tablet or 1 packet of oral granules **once daily** (half of normal dose)

Rifampin Rifabutin Phenobarbital Phenytoin Carbamazepine St. John's wort	CYP3A4 strong inducers	Concurrent use is **NOT** recommended
Grapefruit Juice	CYP3A4 moderate inhibitors	

Lumacaftor/ivacaftor

- Adults and pediatrics age ≥12 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
    - ≥ 14 kg: 1 packet (LUM 150mg/IVA 188mg) every 12 hours
- Hepatic impairment
    - Moderate impairment (Child-Pugh class B):
        - Age ≥ 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 ≥ 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 ≥6 years weighing ≥30 kg : 1 tablet (TEZ 100 mg/IVA 150 mg) in the morning and IVA 150 mg in the evening
- Pediatrics age ≥ 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: *6/21(MH); 6/20 (MH);(9/19); 9/18; 7/18; 11/16; 11/15; 7/15; 5/15; 5/14; 6/12*

Implementation: *7/1/20; 11/1/19; 11/1/2018; 1/1/16; 8/25/15; 8/12*