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, December 3rd, 2020 1:00 - 5:00 PM
Remote Meeting via Zoom Platform
MEETING AGENDA

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

I. CALL TO ORDER

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

A. Quarterly Utilization Reports
B. CMS Annual Report
C. P&T Annual Report
D. Oncology Policy Update
E. Drug Class Literature Scans
   1. Substance Use Disorder, Opioid and Alcohol
   2. Newer Antiemetics
   3. Public Comment

III. DUR ACTIVITIES

1:25 PM	A. ProDUR Report	R. Holsapple (GT)
	B. RetroDUR Report	D. Engen (OSU)
	C. Oregon State Drug Review	K. Sentena (OSU)

1. Optimizing the Use of NPH Insulin in Patients with Type 2 Diabetes Mellitus
2. Shifts in the Treatment of Community Acquired Pneumonia

IV. DUR OLD BUSINESS

1:40 PM	A. LABA/LAMA/ICS Combination Inhaler Prior Authorization Update	K. Sentena (OSU)

1. Prior Authorization Criteria Update
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

1:45 PM	B. Severe Inflammatory Skin Disease HERC Guideline Note and Prior Authorization Update 1. Prior Authorization Criteria Update 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	D. Moretz (OSU)
	V. PREFERRED DRUG LIST NEW BUSINESS	
1:50 PM	A. Sedatives Class Update with New Drug Evaluation 1. Class Update/Prior Authorization Criteria 2. Dayvigo® (lemborexant) New Drug Evaluation 3. Public Comment 4. Discussion of Clinical Recommendations to OHA	A. Gibler (OSU)
2:10 PM	B. Tepezza® (teprotumumab-trbw) New Drug Evaluation 1. New Drug Evaluation/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	S. Fletcher (OSU)
2:25 PM	C. Gout Class Update 1. Class Update/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	K. Sentena (OSU)
2:40 PM	D. Evrysdi™ (risdiplam) New Drug Evaluation 1. New Drug Evaluation/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	D. Engen (OSU)
3:00 PM	BREAK	
3:15 PM	E. Oxervate™ (cenegermin) New Drug Evaluation 1. New Drug Evaluation/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	M. Herink (OSU)
	VI. DUR NEW BUSINESS	
3:30 PM	A. Drug Discontinuation Case Management Policy Proposal 1. Policy Proposal 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	S. Servid (OSU)
3:45 PM	B. Consultation for Antipsychotics in Kids Policy Evaluation 1. Policy Evaluation 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	S. Servid (OSU)

4:00 PM VII. PDL OLD BUSINESS

A. CGRP inhibitors (evidence review conducted in August) K. Sentena (OSU)
   1. No Clinical Recommendations to OHA
   2. Public Comment

4:05 PM VIII. EXECUTIVE SESSION

4:50 PM IX. RECONVENE for PUBLIC RECOMMENDATIONS

X. ADJOURN

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Oregon Pharmacy and Therapeutics Committee – Appointed members

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

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee

Thursday, October 01, 2020 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: Mark Helm, MD, MBA, FAAP; Caryn Mickelson, PharmD; Russell Huffman, DNP, PMHNP; Tracy Klein, PhD, FNP; William Origer, MD; James Slater, PharmD; Stacy Ramirez, PharmD; Cathy Zehrung RPh;

Staff Present: Roger Citron, RPh; David Engen, PharmD; Andrew Gibler, PharmD; Richard Holsapple, RPh; Deanna Moretz, PharmD; Sarah Servid, PharmD; Sara Fletcher, PharmD; Kathy Sentena, PharmD; Dee Weston, JD; Brandon Wells; Jennifer Bowen

Audience: Karen Einbinder, Greenwich Biosciences; Adam Kopp, Zogenix Inc.; Amiee Weems, Acorda Therapeutics; Amy Burns, Allcare; Andrea Wilcuts, Takeda; **Anthony Wheeler, Eli Lilly***; Brandon Yip, Sanofi; Bruce Wallace, Azurity; Camille Kerr, Regeneron; Chi Kohloff, Viela Bio; Christina Hartmann; Dan Allen, Sanofi-Genzyme; Dave Huges; David Nagarkatti-Gude; **Debbie Sheppe, Neurelis*;** Dennis Schaffner, Sanofi-Genzyme; Deron Grothe, Teva Pharmaceuticals; Elise Conlee, Greenwich Boisciences; Jena Ritter; Jeanne Vander Zanded; Jeffery Mussack, Braeburn Inc.; **Jennifer Shear, Teva*;** Kaite Scheelar; Keely Larson, Bayer Healthcare; Kim Tran; Lori Howarth, Bayer; Lori McDermott, Supernus; **Margaret Olmon, AbbVie*;** Marissa Tabile; Mark Kantor, AllCare; Timothy McFerron, Alkermes; Michael Fifer, Providence; Michael Foster, BMS; Nena Hartman, Neurocrine Biosciences; Nick Kashey; **Carrie Johnson, Amgen*;** Nichole Robline, Otsuka; Paul Thompson, Alkermes; Robb Host Neurelis; Robin Traver, Umpquah Health; Roy Lindfield, Sunovion; Shannon Lee, Trillium; **Shirley Quach, Novartis*; Sibin Stephen, Zogenix***; **Stephanie Kennedy, Greenwich Biosciences***; Suzanne Gauen, Providence; Terry Cadenasso, Acorda Therapeutics; Venus Holder, Eli Lilly; **William O'Neill, Sunovion*;** Amanda Parrish

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(*) Provided verbal testimony

Written testimony: Posted to OSU Website

I. CALL TO ORDER

A. The meeting was called to order at approximately 1:05 pm. Introductions were made by Committee members and staff
B. Conflict of Interest Declaration - No new conflicts of interest were declared
C. Approval of August 2020 minutes presented by Mr. Citron
ACTION: Motion to approve, 2nd, all in favor
D. Department Update provided by Dee Weston
E. Covid-19 Updates

II. CONSENT AGENDA TOPICS

A. Oncology Policy Update
B. Orphan Drug Policy Update
ACTION: Motion to approve, 2nd, all in favor

III. DUR NEW BUSINESS

A. Bipolar Drug Use Evaluation (DUE)
Doctors Nick Kashey, MD and David Nagarkatti-Gude, MD from the Mental Health Clinical Advisory Group (MHCAG) presented the MHCAG Acute Bipolar Depression and Acute Bipolar Mania treatment algorithms.

Doctor Sarah Servid, PharmD presented the Bipolar DUE and proposal to:

1. Implement a targeted profiled review of patients with bipolar disorder who have frequent hospitalization or emergency room visits for psychiatric reasons to identify areas for optimization of medications and notify prescribers if opportunities to improve care are identified
2. Prioritize patients with 3 or more hospitalizations or ED visits over 6 months for psychiatric reasons and who: 1) appear non-adherent to current therapy; or 2) are prescribed regimens not recommended by the OHA and Mental Health Clinical Advisory Group. Non-recommended regimens may include patients with 3 or more bipolar medications, patients prescribed antidepressant monotherapy, or patients who use aripiprazole for bipolar depression

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

IV. PREFERRED DRUG LIST NEW BUSINESS

A. Atopic Dermatitis (AD) Literature Scan
Dr. Moretz presented the proposal to:

1. Revise the prior authorization (PA) criteria for AD and topical antipsoriatics to reflect the expanded indication for crisaborole in children aged 3 months and older with moderate AD
2. Revise the PA criteria for dupilumab to reflect expanded indication for management of moderate-to severe AD not well controlled by topical prescription medications in children older than 6 years of age

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

B. Asthma COPD Class Update
Dr. Sentena presented the proposal to:

1. Make no changes to the PMPDP based on clinical evidence
2. Update the clinical definition of severe and very severe COPD in the roflumilast PA criteria
3. Clarify the age recommendations for use of monoclonal antibodies

Public Comment: Jennifer Shear, Teva Pharmaceuticals

ACTION: The Committee amended he proposed Roflumilast PA criteria to include that the request be from or in consultation with pulmonary specialist
Motion to approve, 2nd, all in favor

C. Antiepileptic (non-injectable) Class Update and New Drug Evaluation (NDE)
Dr. Moretz presented the proposal to:

1. Designate fenfluramine as non-preferred on the PMPDP and to implement the proposed PA criteria to ensure medically appropriate utilization
2. Revise the PA criteria for cannabidiol to reflect the expanded indication and appropriate dosing for tuberous sclerosis complex (TSC) in patients 1 year of age and older
3. Rename Antiepileptics class from “oral and rectal” to “non-injectable” to account for nasal formulations

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Public Comments: Sibin Stephen, Zogenix; Debbie Sheppe, Neurelis; Stephanie Kennedy Greenwich Biosciences

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

D. Antacids: Proton Pump Inhibitors and H2 Receptor Antagonists Class Update
Dr.Sentena presented the proposal to:

1. Make no changes to the PMPDP based on clinical evidence
2. Modify PPI PA criteria to clarify durations of therapy

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

E. Parkinson's Disease Class Update and NDEs
Dr. Gibler presented the proposal to:

1. Designate istradefylline, opicapone and apomorphine sublingual as a non-preferred on the PMPDP based on the clinical evidence and availability of several first-line agents
2. Update the Anti-Parkinson's Agents PA criteria to ensure safe and appropriate use of the new agents

Public Comment: William O'Neill, Sunovion Pharmaceuticals

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

F. Biologics for Autoimmune Conditions DERP Summary and Policy Evaluation
Dr.Moretz presented the DERP summary and proposal to:

1. Make no changes to the PMPDP based on clinical evidence
2. Modify the PA criteria to reflect updated indications for the Targeted Immune Modulator agents as proposed

Dr. Servid presented the Policy Evaluation and recommended:

1. Make no policy changes based on current utilization data
2. Continue to monitor trends in utilization

Public Comment: Shirley Quach, Novartis; Margaret Olmon, AbbVie; Anthony Wheeler, Eli Lilly; Carrie Johnson, Amgen

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

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V. DUR NEW BUSINESS (continued)

B. Modafinil/armodafinil Drug Use Evaluation (DUE)
ACTION: Committee reviewed the DUE and recommended modifying the modafinil/armodafinil PA criteria to prevent inappropriate use during pregnancy and in women of childbearing age.
ACTION: Motion to approve, 2nd, all in favor

VI. EXECUTIVE SESSION

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

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Staff Present: Roger Citron, RPh; David Engen, PharmD; Richard Holsapple, RPh; Deanna Moretz, PharmD; Sarah Servid, PharmD; Sara Fletcher, PharmD; Kathy Sentena, PharmD; Dee Weston, JD; Brandon Wells; Jennifer Bowen

VII. RECONVENE for PUBLIC RECOMMENDATIONS

A. Parkinson's Disease Class Update and NDEs:
Recommendation: Make amantadine capsules and tablets preferred
ACTION: Motion to approve, 2nd, all in favor

B. Asthma/COPD Class Update
Recommendation: Make Tudorza® Pressair non-preferred and make AirDuo RespiClick®, Anoro Ellipta, and Stiolto® Respimat® preferred

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

C. Antiepileptics (non-injectable) Class Update and NDE
Recommendation: make fenfluramine non-preferred
ACTION: **Motion to approve, 2nd, all in favor**

D. PPI and H2Ras Update
Recommendation: Make famotidine complete chew tablets nizatidine solution, Aciphex®, Dexilant ®, Prevacid® DR capsules , and Pylera™ and lansopra/amoxicil/clarithro combo pack preferred

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

E. Atopic Dermatitis Literature Scan
Recommendation: Make no changes to the PMPDP
ACTION: Motion to approve, 2nd, all in favor

F. Biologics for Autoimmune Conditions
Recommendation: Make secukinumab non-preferred

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

IX. ADJOURN

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Pharmacy Utilization Summary Report: April 2019 - March 2020

Eligibility	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Avg Monthly
Total Members (FFS & Encounter)	981,514	979,468	979,316	980,226	981,629	983,778	985,585	983,689	987,294	994,279	996,305	1,000,312	986,116
FFS Members	113,342	112,672	115,232	91,378	99,920	100,302	93,871	98,749	99,972	99,615	99,252	99,928	102,019
OHP Basic with Medicare	28,706	29,057	29,456	8,912	9,279	9,365	9,067	9,362	9,174	8,622	8,495	7,620	13,926
OHP Basic without Medicare	11,739	11,877	12,010	11,793	11,967	12,047	11,869	12,431	12,040	11,882	11,860	11,739	11,938
ACA	72,897	71,738	73,766	70,673	78,674	78,890	72,935	76,956	78,758	79,111	78,897	80,569	76,155
Encounter Members	868,172	866,796	864,084	888,848	881,709	883,476	891,714	884,940	887,322	894,664	897,053	900,384	884,097
OHP Basic with Medicare	48,472	48,276	48,107	68,815	68,626	68,722	69,151	68,769	69,265	69,949	70,261	71,185	64,133
OHP Basic without Medicare	62,066	61,919	61,721	61,928	61,667	61,560	62,079	62,180	62,716	62,920	62,837	62,961	62,213
ACA	757,634	756,601	754,256	758,105	751,416	753,194	760,484	753,991	755,341	761,795	763,955	766,238	757,751

Gross Cost Figures for Drugs	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	YTD Sum
Total Amount Paid (FFS & Encounter)	$84,561,129	$85,980,028	$78,167,189	$85,055,814	$83,123,535	$79,456,672	$88,365,709	$78,985,841	$84,952,890	$88,322,009	$83,247,202	$97,428,147	$1,017,646,165
Mental Health Carve-Out Drugs	$8,447,557	$8,554,692	$7,894,004	$8,770,843	$8,637,006	$8,054,406	$8,946,623	$8,123,302	$8,833,011	$9,313,993	$8,618,548	$9,530,946	$103,724,932
OHP Basic with Medicare	$5,313	$9,126	$19,504	$33,196	$41,678	$32,600	$39,134	$33,985	$42,387	$39,720	$32,707	$32,473	$361,823
OHP Basic without Medicare	$3,368,793	$3,391,609	$3,114,862	$3,469,040	$3,404,521	$3,092,348	$3,526,687	$3,185,572	$3,467,289	$3,664,083	$3,322,058	$3,685,725	$40,692,588
ACA	$5,008,598	$5,091,642	$4,710,878	$5,218,235	$5,140,367	$4,887,029	$5,333,566	$4,861,088	$5,268,846	$5,554,566	$5,206,509	$5,754,480	$62,035,805
FFS Physical Health Drugs	$2,879,553	$2,931,558	$2,704,342	$2,766,861	$2,695,478	$2,464,425	$2,876,750	$2,555,405	$2,680,436	$3,080,244	$2,756,464	$3,063,379	$33,454,895
OHP Basic with Medicare	$252,462	$213,421	$172,138	$54,037	$55,005	$55,104	$56,836	$56,626	$59,356	$63,798	$53,297	$59,705	$1,151,784
OHP Basic without Medicare	$913,628	$976,791	$992,631	$1,090,552	$977,844	$864,722	$1,097,580	$861,451	$915,077	$1,113,467	$1,001,354	$1,084,160	$11,889,257
ACA	$1,579,955	$1,598,242	$1,436,366	$1,522,871	$1,534,551	$1,430,300	$1,598,719	$1,523,079	$1,593,255	$1,766,011	$1,581,027	$1,780,399	$18,944,775
FFS Physician Administered Drugs	$1,480,691	$1,549,242	$1,881,057	$1,182,623	$1,281,658	$1,525,455	$1,511,969	$1,399,813	$1,262,100	$1,406,300	$1,647,684	$1,481,560	$17,610,151
OHP Basic with Medicare	$373,120	$394,329	$342,177	$129,304	$178,107	$164,039	$184,137	$144,037	$145,078	$151,072	$123,996	$97,255	$2,426,651
OHP Basic without Medicare	$248,526	$241,896	$571,302	$191,329	$158,834	$571,313	$412,645	$381,235	$218,817	$202,571	$558,507	$255,867	$4,012,843
ACA	$435,887	$478,336	$564,674	$360,353	$512,532	$412,295	$409,614	$497,868	$467,315	$610,371	$511,420	$404,709	$5,665,374
Encounter Physical Health Drugs	$57,531,834	$58,011,804	$52,064,337	$56,710,022	$55,852,143	$53,801,689	$59,496,847	$53,103,585	$56,842,562	$58,214,720	$55,183,721	$65,718,370	$682,531,635
OHP Basic with Medicare	$297,613	$358,530	$565,673	$770,940	$713,674	$731,917	$818,160	$757,098	$714,018	$851,925	$715,087	$844,014	$8,138,649
OHP Basic without Medicare	$14,411,598	$14,591,538	$13,246,587	$13,892,922	$13,434,217	$12,770,370	$14,341,487	$13,213,012	$14,164,763	$14,118,233	$13,288,441	$15,375,219	$166,848,387
ACA	$42,137,890	$42,410,915	$37,648,008	$41,394,985	$41,101,073	$39,674,389	$43,722,283	$38,596,448	$41,297,272	$42,564,664	$40,567,827	$48,714,629	$499,830,384
Encounter Physician Administered Drugs	$14,221,494	$14,932,731	$13,623,450	$15,625,466	$14,657,250	$13,610,696	$15,533,520	$13,803,736	$15,334,781	$16,306,751	$15,040,785	$17,633,892	$180,324,552
OHP Basic with Medicare	$326,967	$376,244	$323,347	$565,456	$495,483	$555,523	$599,925	$562,445	$552,790	$575,235	$560,588	$561,137	$6,055,140
OHP Basic without Medicare	$3,130,179	$3,440,733	$2,896,279	$2,930,664	$3,028,602	$2,743,246	$3,346,156	$2,704,265	$3,236,489	$3,626,398	$3,690,116	$3,443,051	$38,216,178
ACA	$10,551,544	$10,902,548	$10,249,304	$11,704,067	$10,809,620	$10,005,193	$11,262,850	$10,076,696	$11,019,283	$11,669,496	$10,521,344	$13,401,591	$132,173,536

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

Last Updated: October 22, 2020

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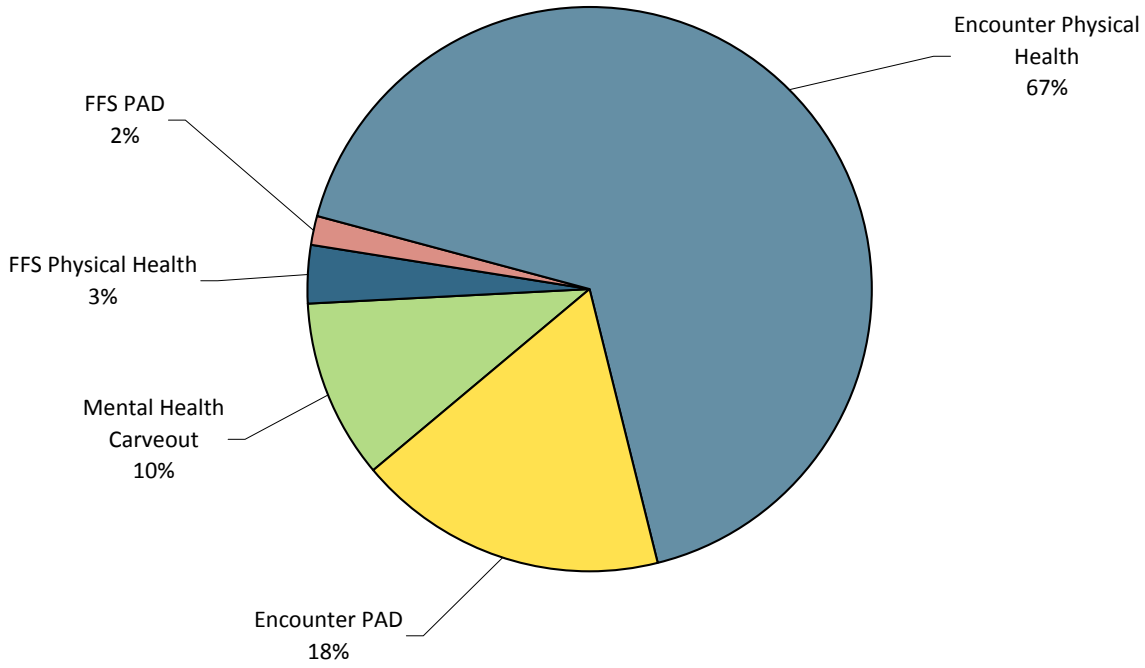
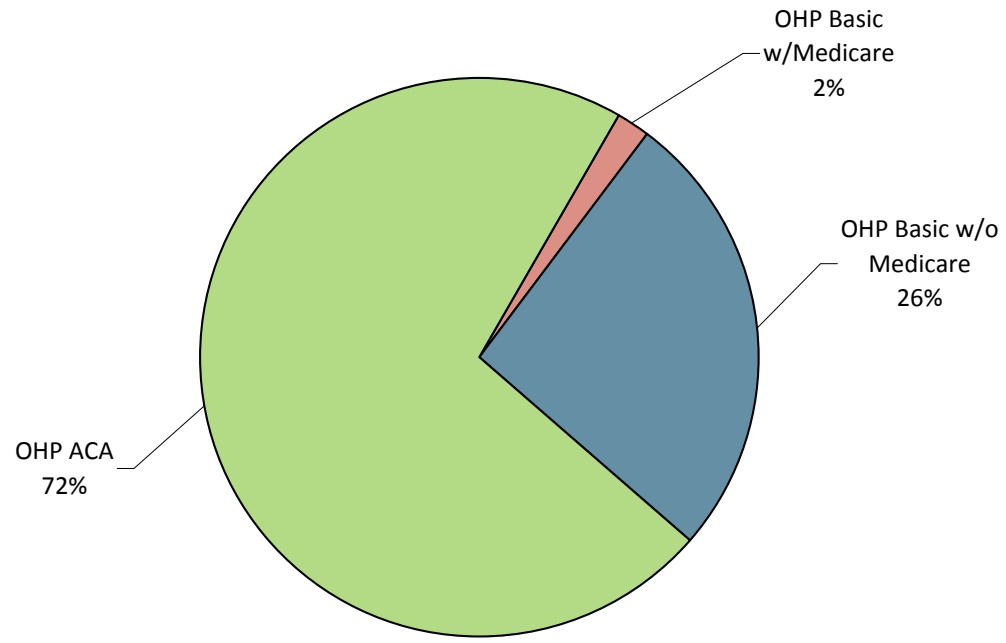
Pharmacy Utilization Summary Report: April 2019 - March 2020

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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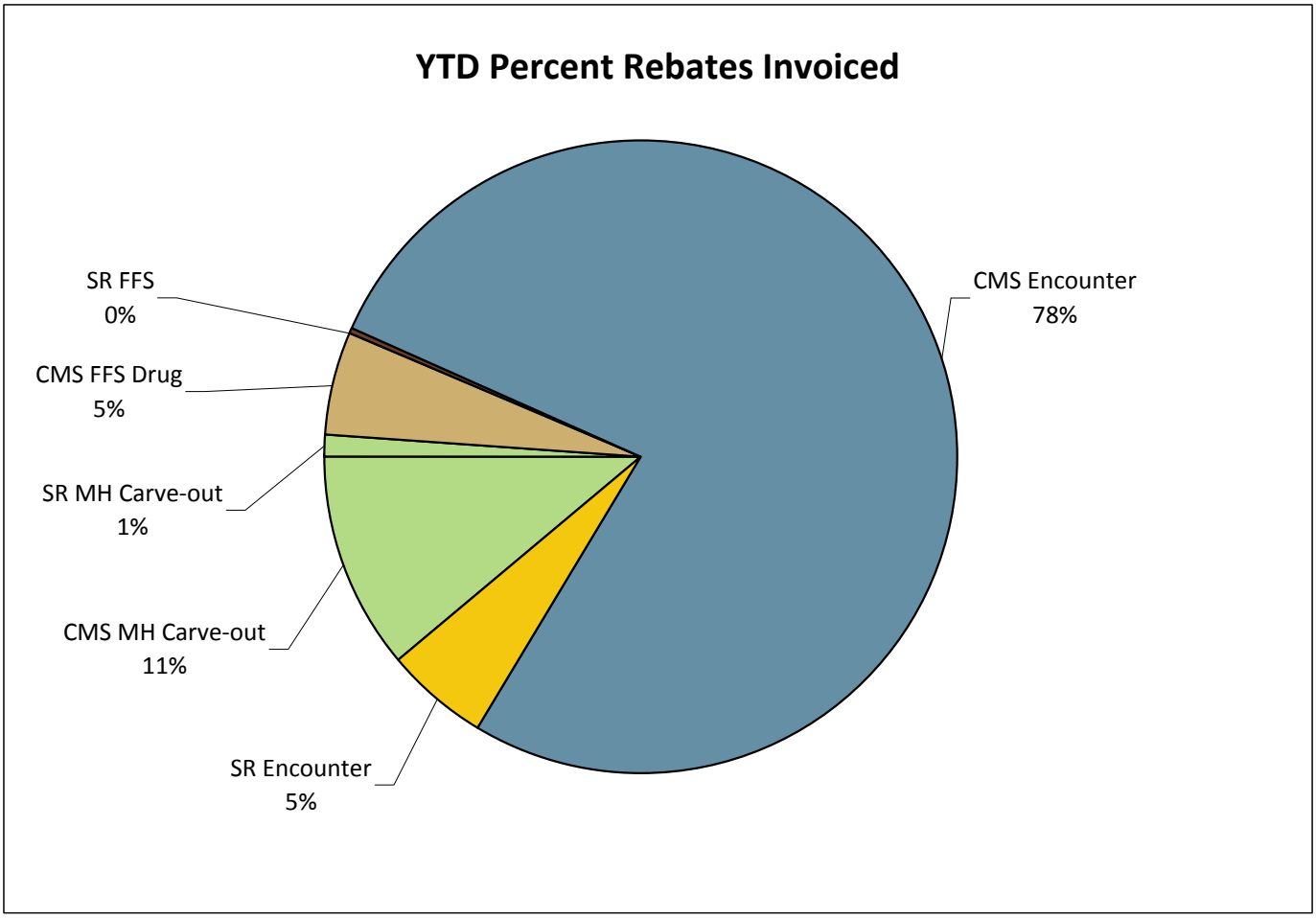
Pharmacy Utilization Summary Report: April 2019 - March 2020

Quarterly Rebates Invoiced	2019-Q2	2019-Q3	2019-Q4	2020-Q1	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$106,429,227	$105,097,256	$104,686,174	$113,955,839	$430,168,495
CMS MH Carve-out	$11,355,244	$11,213,311	$11,473,116	$13,675,140	$47,716,811
SR MH Carve-out	$1,120,422	$1,156,887	$1,270,415	$1,414,199	$4,961,924
CMS FFS Drug	$6,007,808	$5,079,370	$4,990,931	$6,060,878	$22,138,988
SR FFS	$307,417	$304,047	$332,895	$424,577	$1,368,936
CMS Encounter	$81,536,784	$82,502,401	$81,463,483	$85,459,231	$330,961,899
SR Encounter	$6,101,551	$4,841,239	$5,155,334	$6,921,814	$23,019,938

Quaterly Net Drug Costs	2019-Q2	2019-Q3	2019-Q4	2020-Q1	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$142,279,120	$142,538,766	$147,618,267	$155,041,518	$587,477,670
Mental Health Carve-Out Drugs	$12,420,587	$13,092,057	$13,159,405	$12,374,148	$51,046,197
FFS Phys Health + PAD	$7,111,217	$6,533,083	$6,962,647	$6,950,176	$27,557,122
Encounter Phys Health + PAD	$122,747,316	$122,913,625	$127,496,215	$135,717,194	$508,874,350



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

Last Updated: October 22, 2020

Drug Use Research & Management Program
DHS - Health Systems Division
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Pharmacy Utilization Summary Report: April 2019 - March 2020

Gross PMPM Drug Costs (Rebates not Subtracted)	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$86.15	$87.78	$79.82	$86.77	$84.68	$80.77	$89.66	$80.30	$86.05	$88.83	$83.56	$97.40	$85.98
Mental Health Carve-Out Drugs	$8.61	$8.73	$8.06	$8.95	$8.80	$8.19	$9.08	$8.26	$8.95	$9.37	$8.65	$9.53	$8.76
FFS Physical Health Drugs	$25.41	$26.02	$23.47	$30.28	$26.98	$24.57	$30.65	$25.88	$26.81	$30.92	$27.77	$30.66	$27.45
FFS Physician Administered Drugs	$13.06	$13.75	$16.32	$12.94	$12.83	$15.21	$16.11	$14.18	$12.62	$14.12	$16.60	$14.83	$14.38
Encounter Physical Health Drugs	$66.27	$66.93	$60.25	$63.80	$63.35	$60.90	$66.72	$60.01	$64.06	$65.07	$61.52	$72.99	$64.32
Encounter Physician Administered Drugs	$16.38	$17.23	$15.77	$17.58	$16.62	$15.41	$17.42	$15.60	$17.28	$18.23	$16.77	$19.58	$16.99

Claim Counts	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Avg Monthly
Total Claim Count (FFS & Encounter)	1,076,941	1,087,649	1,004,370	1,070,887	1,050,042	1,028,418	1,105,169	1,007,039	1,079,018	1,111,384	1,040,531	1,142,814	1,067,022
Mental Health Carve-Out Drugs	162,582	163,473	151,536	165,175	161,570	156,903	167,866	154,111	164,605	169,884	157,763	177,094	162,714
FFS Physical Health Drugs	56,939	56,897	51,182	43,094	42,359	41,650	43,812	39,776	42,307	46,490	42,231	45,925	46,055
FFS Physician Administered Drugs	13,975	14,721	13,419	12,467	12,079	11,527	12,023	10,443	11,568	12,833	11,166	9,977	12,183
Encounter Physical Health Drugs	727,514	734,360	676,149	725,940	708,037	698,124	755,330	683,402	734,583	759,144	714,273	806,921	726,981
Encounter Physician Administered Drugs	115,931	118,198	112,084	124,211	125,997	120,214	126,138	119,307	125,955	123,033	115,098	102,897	119,089

Gross Amount Paid per Claim (Rebates not Subtracted)	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$78.52	$79.05	$77.83	$79.43	$79.16	$77.26	$79.96	$78.43	$78.73	$79.47	$80.00	$85.25	$79.42
Mental Health Carve-Out Drugs	$51.96	$52.33	$52.09	$53.10	$53.46	$51.33	$53.30	$52.71	$53.66	$54.83	$54.63	$53.82	$53.10
FFS Physical Health Drugs	$50.57	$51.52	$52.84	$64.21	$63.63	$59.17	$65.66	$64.24	$63.36	$66.26	$65.27	$66.70	$61.12
FFS Physician Administered Drugs	$105.95	$105.24	$140.18	$94.86	$106.11	$132.34	$125.76	$134.04	$109.10	$109.58	$147.56	$148.50	$121.60
Encounter Physical Health Drugs	$79.08	$79.00	$77.00	$78.12	$78.88	$77.07	$78.77	$77.70	$77.38	$76.68	$77.26	$81.44	$78.20
Encounter Physician Administered Drugs	$122.67	$126.34	$121.55	$125.80	$116.33	$113.22	$123.15	$115.70	$121.75	$132.54	$130.68	$171.37	$126.76

Gross Amount Paid per Claim - Generic-Multi Source Drugs (Rebates not Subtracted)	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Avg Monthly
Generic-Multi Source Drugs: Average Paid / Claim (FFS & Encounter)	$18.76	$18.88	$18.75	$19.18	$19.35	$19.24	$19.46	$18.83	$19.04	$19.47	$19.73	$20.07	$19.23
Mental Health Carve-Out Drugs	$17.96	$18.15	$18.23	$18.40	$18.21	$17.41	$17.52	$17.57	$17.69	$17.54	$17.51	$16.67	$17.74
FFS Physical Health Drugs	$17.95	$17.18	$17.60	$19.09	$19.76	$19.17	$21.32	$20.59	$20.07	$21.11	$19.79	$20.10	$19.48
Encounter Physical Health Drugs	$19.02	$19.17	$18.96	$19.39	$19.61	$19.71	$19.85	$19.05	$19.32	$19.85	$20.27	$20.89	$19.59

Gross Amount Paid per Claim - Branded-Single Source Drugs (Rebates not Subtracted)	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Avg Monthly
Branded-Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$478.93	$484.89	$476.69	$494.72	$503.42	$466.74	$468.64	$487.98	$497.93	$500.18	$508.85	$524.66	$491.14
Mental Health Carve-Out Drugs	$1,068.47	$1,064.26	$1,064.09	$1,078.09	$1,073.36	$1,048.18	$1,074.34	$1,059.42	$1,063.74	$1,103.03	$1,094.60	$1,104.73	$1,074.69
FFS Physical Health Drugs	$170.55	$179.74	$188.98	$262.08	$260.31	$230.88	$252.41	$256.44	$248.95	$265.92	$275.00	$272.00	$238.61
Encounter Physical Health Drugs	$485.89	$491.05	$478.40	$480.72	$490.00	$454.30	$452.84	$473.63	$484.72	$483.95	$492.33	$511.01	$481.57

Generic Drug Use Percentage	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Avg Monthly
Generic Drug Use Percentage	88.3%	88.4%	88.5%	88.7%	88.8%	88.3%	87.9%	88.5%	88.8%	89.0%	89.2%	88.9%	88.6%
Mental Health Carve-Out Drugs	96.8%	96.7%	96.8%	96.7%	96.7%	96.7%	96.6%	96.6%	96.6%	96.6%	96.6%	96.6%	96.7%
FFS Physical Health Drugs	78.6%	78.9%	79.4%	81.4%	81.8%	81.1%	80.8%	81.5%	81.1%	81.6%	82.2%	81.5%	80.8%
Encounter Physical Health Drugs	87.1%	87.3%	87.4%	87.3%	87.4%	86.8%	86.4%	87.1%	87.5%	87.8%	87.9%	87.6%	87.3%

Preferred Drug Use Percentage	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19	Oct-19	Nov-19	Dec-19	Jan-20	Feb-20	Mar-20	Avg Monthly
Preferred Drug Use Percentage	85.54%	85.52%	85.46%	85.42%	85.34%	85.26%	85.05%	85.44%	85.50%	85.21%	85.11%	85.19%	85.3%
Mental Health Carve-Out Drugs	73.66%	73.51%	73.26%	73.19%	73.18%	73.24%	73.31%	73.11%	73.03%	73.13%	73.06%	73.28%	73.2%
FFS Physical Health Drugs	95.23%	95.24%	95.48%	94.50%	94.58%	94.58%	94.56%	94.68%	94.97%	94.72%	94.32%	93.75%	94.7%
Encounter Physical Health Drugs	87.47%	87.47%	87.46%	87.65%	87.56%	87.43%	87.15%	87.71%	87.78%	87.35%	87.26%	87.31%	87.5%

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

Last Updated: October 22, 2020

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

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	LATUDA	Antipsychotics, 2nd Gen	$6,480,755	17.1%	5,235	$1,238	Y
2	INVEGA SUSTENNA	Antipsychotics, Parenteral	$3,006,102	7.9%	1,489	$2,019	Y
3	VRAYLAR	Antipsychotics, 2nd Gen	$2,295,119	6.0%	2,038	$1,126	Y
4	REXULTI	Antipsychotics, 2nd Gen	$1,580,505	4.2%	1,465	$1,079	V
5	ABILIFY MAINTENA	Antipsychotics, Parenteral	$1,572,282	4.1%	808	$1,946	Y
6	INVEGA TRINZA	Antipsychotics, Parenteral	$803,809	2.1%	126	$6,379	Y
7	ARISTADA	Antipsychotics, Parenteral	$675,631	1.8%	297	$2,275	Y
8	TRINTELLIX	Antidepressants	$628,630	1.7%	1,566	$401	V
9	BUPROPION XL	Antidepressants	$569,730	1.5%	30,660	$19	V
10	SAPHRIS	Antipsychotics, 2nd Gen	$547,644	1.4%	771	$710	Y
11	SERTRALINE HCL	Antidepressants	$514,512	1.4%	50,029	$10	Y
12	VIIBRYD	Antidepressants	$503,535	1.3%	1,703	$296	V
13	DULOXETINE HCL	Antidepressants	$470,214	1.2%	32,608	$14	V
14	FLUOXETINE HCL	Antidepressants	$454,474	1.2%	36,382	$12	Y
15	TRAZODONE HCL	Antidepressants	$433,171	1.1%	42,882	$10	
16	PALIPERIDONE ER	Antipsychotics, 2nd Gen	$373,326	1.0%	1,923	$194	V
17	ESCITALOPRAM OXALATE	Antidepressants	$318,523	0.8%	31,222	$10	Y
18	VENLAFAXINE HCL ER	Antidepressants	$309,965	0.8%	1,977	$157	V
19	RISPERDAL CONSTA*	Antipsychotics, Parenteral	$301,561	0.8%	340	$887	Y
20	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	$296,142	0.8%	21,847	$14	
21	ATOMOXETINE HCL*	ADHD Drugs	$286,659	0.8%	5,250	$55	Y
22	LAMOTRIGINE	Antiepileptics (non-injectable)	$274,628	0.7%	25,658	$11	Y
23	BIKTARVY	HIV	$273,915	0.7%	102	$2,685	Y
24	CHOLBAM*	Bile Therapy	$248,996	0.7%	6	$41,499	N
25	LAMOTRIGINE ER	Antiepileptics (non-injectable)	$235,354	0.6%	2,385	$99	V
26	Inj Pembrolizumab	Physican Administered Drug	$226,615	0.6%	48	$4,721	
27	VENLAFAXINE HCL ER	Antidepressants	$215,620	0.6%	16,774	$13	Y
28	AMITRIPTYLINE HCL*	Antidepressants	$206,699	0.5%	14,466	$14	Y
29	QUETIAPINE FUMARATE*	Antipsychotics, 2nd Gen	$206,503	0.5%	17,946	$12	Y
30	Inj, Nusinersen, 0.1mg	Physican Administered Drug	$199,020	0.5%	1	$199,020	
31	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$198,234	0.5%	19	$10,433	Y
32	TRIKAFTA*	Cystic Fibrosis	$191,447	0.5%	21	$9,117	N
33	CITALOPRAM HBR	Antidepressants	$187,607	0.5%	21,274	$9	Y
34	LANTUS SOLOSTAR*	Diabetes, Insulins	$182,939	0.5%	467	$392	Y
35	Gammagard Liquid Injection	Physican Administered Drug	$172,442	0.5%	25	$6,898	
36	ARIPIPRAZOLE	Antipsychotics, 2nd Gen	$168,671	0.4%	11,197	$15	V
37	HUMIRA(CF) PEN*	Biologics for Autoimmune Conditions	$154,037	0.4%	34	$4,531	Y
38	CHLORPROMAZINE HCL	Antipsychotics, 1st Gen	$153,848	0.4%	615	$250	V
39	MIRTAZAPINE	Antidepressants	$150,954	0.4%	9,747	$15	Y
40	OLANZAPINE	Antipsychotics, 2nd Gen	$145,914	0.4%	11,229	$13	Y
		Top 40 Aggregate:	**$26,215,732**		**402,632**	**$7,465**	
		All FFS Drugs Totals:	**$37,977,894**		**648,363**	**$619**	

*** Drug requires Prior Authorization**

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

Last updated: October 22, 2020

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

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	BIKTARVY	HIV	$273,915	2.7%	102	$2,685	Y
2	CHOLBAM*	Bile Therapy	$248,996	2.5%	6	$41,499	N
3	Inj Pembrolizumab	Physican Administered Drug	$226,615	2.3%	48	$4,721	
4	Inj, Nusinersen, 0.1mg	Physican Administered Drug	$199,020	2.0%	1	$199,020	
5	MAVYRET*	Hepatitis C, Direct-Acting Antivirals	$198,234	2.0%	19	$10,433	Y
6	TRIKAFTA*	Cystic Fibrosis	$191,447	1.9%	21	$9,117	N
7	LANTUS SOLOSTAR*	Diabetes, Insulins	$182,939	1.8%	467	$392	Y
8	Gammagard Liquid Injection	Physican Administered Drug	$172,442	1.7%	25	$6,898	
9	HUMIRA(CF) PEN*	Biologics for Autoimmune Conditions	$154,037	1.5%	34	$4,531	Y
10	CONCERTA*	ADHD Drugs	$144,666	1.4%	526	$275	N
11	STELARA*	Biologics for Autoimmune Conditions	$134,653	1.3%	15	$8,977	N
12	Epoetin Alfa, 100 Units Esrd	Physican Administered Drug	$132,528	1.3%	589	$225	
13	PROMACTA	Thrombocytopenia Drugs	$111,662	1.1%	10	$11,166	Y
14	Inj., Emicizumab-Kxwh 0.5 Mg	Physican Administered Drug	$109,387	1.1%	4	$27,347	
15	BUPRENORPHINE-NALOXONE*	Substance Use Disorders, Opioid & Alcohol	$101,727	1.0%	1,694	$60	Y
16	VYVANSE*	ADHD Drugs	$100,999	1.0%	623	$162	Y
17	Inj., Rituximab, 10 Mg	Physican Administered Drug	$93,276	0.9%	34	$2,743	
18	VIMPAT	Antiepileptics (non-injectable)	$92,680	0.9%	200	$463	Y
19	ALBUTEROL SULFATE HFA	Beta-Agonists, Inhaled Short-Acting	$90,744	0.9%	2,482	$37	Y
20	ELIQUIS	Anticoagulants, Oral and SQ	$90,066	0.9%	280	$322	Y
21	Aflibercept Injection	Physican Administered Drug	$89,903	0.9%	156	$576	
22	EPCLUSA*	Hepatitis C, Direct-Acting Antivirals	$80,945	0.8%	4	$20,236	Y
23	Etonogestrel Implant System	Physican Administered Drug	$80,142	0.8%	130	$616	
24	NOVOLOG FLEXPEN	Diabetes, Insulins	$74,394	0.7%	136	$547	Y
25	LEVEMIR FLEXTOUCH	Diabetes, Insulins	$72,608	0.7%	140	$519	Y
26	FLOVENT HFA	Corticosteroids, Inhaled	$71,713	0.7%	452	$159	Y
27	ENBREL SURECLICK*	Biologics for Autoimmune Conditions	$71,075	0.7%	25	$2,843	Y
28	VIGABATRIN	Antiepileptics (non-injectable)	$69,683	0.7%	6	$11,614	N
29	Infliximab Not Biosimil 10mg	Physican Administered Drug	$66,949	0.7%	55	$1,217	
30	XULANE	STC 63 - Oral Contraceptives	$63,532	0.6%	376	$169	
31	PULMOZYME	Cystic Fibrosis	$62,476	0.6%	33	$1,893	Y
32	COSENTYX PEN (2 PENS)*	Biologics for Autoimmune Conditions	$62,453	0.6%	11	$5,678	Y
33	Inj. Pemetrexed Nos 10mg	Physican Administered Drug	$61,965	0.6%	30	$2,065	
34	TRUVADA	HIV	$61,783	0.6%	46	$1,343	Y
35	OPSUMIT*	Pulmonary Arterial Hypertension Oral and Inhale	$60,584	0.6%	6	$10,097	N
36	GENVOYA	HIV	$60,227	0.6%	22	$2,738	Y
37	Mirena, 52 Mg	Physican Administered Drug	$59,480	0.6%	98	$607	
38	HUMIRA*	Biologics for Autoimmune Conditions	$59,335	0.6%	8	$7,417	Y
39	LANTUS	Diabetes, Insulins	$59,291	0.6%	182	$326	Y
40	Injection, Ocrelizumab, 1 Mg	Physican Administered Drug	$58,943	0.6%	4	$14,736	
		Top 40 Aggregate:	**$4,397,515**		**9,100**	**$10,412**	
		All FFS Drugs Totals:	**$9,979,557**		**127,433**	**$640**	

*** Drug requires Prior Authorization**

Notes
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- PDL Key: Y=Preferred, N=Non-Preferred, V=Voluntary, Blank=Non PDL Class
- Amount Paid on the Claim = 1) Ingredient Cost ([AAAC/NADAC/WAC] x Dispense Quantity) + Dispensing Fee. If Billed Amount is lower, pay Billed Amount, 2) - TPL amount

Last updated: October 22, 2020

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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

Brand Name	Generic Name
GAVRETO	pralsetinib

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 11/03/2020)

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
atezolizumab	TECENTRIQ
avapritinib	AYVAKIT
avelumab	BAVENCIO
axicabtagene ciloleucel	YESCARTA
axitinib	INLYTA
belinostat	BELEODAQ
bendamustine HCl	BENDAMUSTINE HCL
bendamustine HCl	BENDEKA
bendamustine HCl	TREANDA
binimetinib	MEKTOVI
belantamab mafodotin-blmf	BLENREP
blinatumomab	BLINCYTO
bosutinib	BOSULIF
brentuximab vedotin	ADCETRIS
brexucabtagene autoleucel	TECARTUS
brigatinib	ALUNBRIG

Generic Name	Brand Name
afatinib dimaleate	GILOTRIF
alectinib HCl	ALECENSA
alpelisib	PIQRAY
apalutamide	ERLEADA
asparaginase (Erwinia chrysan)	ERWINAZE
ipilimumab	YERVOY
Isatuximab	SARCLISA
ivosidenib	TIBSOVO
ixazomib citrate	NINLARO
larotrectinib	VITRAKVI
lenvatinib mesylate	LENVIMA
lorlatinib	LORBRENA
lurbinectedin	ZEPZELCA
lutetium Lu 177 dotate	LUTATHERA
midostaurin	RYDAPT
moxetumomab pasudotox-tdfk	LUMOXITI
necitumumab	PORTRAZZA
neratinib maleate	NERLYNX
niraparib tosylate	ZEJULA
nivolumab	OPDIVO
obinutuzumab	GAZYVA

cabazitaxel	JEVTANA
cabozantinib s-malate	CABOMETYX
cabozantinib s-malate	COMETRIQ
calaspargase pegol-mknl	ASPARLAS
capmatinib	TABRECTA
carfilzomib	KYPROLIS
cemiplimab-rwlc	LIBTAYO
ceritinib	ZYKADIA
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
dinutuximab	UNITUXIN
durvalumab	IMFINZI
duvelisib	COPIKTRA
elotuzumab	EMPLICITI
enasidenib mesylate	IDHIFA
encorafenib	BRAFTOVI
enfortumab vedotin-ejfv	PADCEV
entrectinib	ROZLYTREK
enzalutamide	XTANDI
erdafitinib	BALVERSA
eribulin mesylate	HALAVEN
everolimus	AFINITOR
everolimus	AFINITOR DISPERZ
fam-trastuzumab deruxtecan-nxki	ENHERTU
fedratinib	INREBIC
gilteritinib	XOSPATA
glasdegib	DAURISMO
ibrutinib	IMBRUVICA
idelalisib	ZYDELIG
ingenol mebutate	PICATO
inotuzumab ozogamicin	BESPONSA
trastuzumab-pkrb	HERZUMA

ofatumumab	ARZERRA
olaparib	LYNPARZA
olaratumab	LARTRUVO
omacetaxine mepesuccinate	SYNRIBO
osimertinib mesylate	TAGRISSO
palbociclib	IBRANCE
panobinostat lactate	FARYDAK
pazopanib HCl	VOTRIENT
pembrolizumab	KEYTRUDA
pemigatinib	PEMAZYRE
pertuzumab	PERJETA
pertuzumab/trastuzumab/ haluronidase-zzxf	PHESGO
pexidartinib	TURALIO
polatuzumab vedotin-piiq	POLIVY
pomalidomide	POMALYST
pralatrexate	FOLOTYN
pralsetinib	GAVRETO
ramucirumab	CYRAMZA
regorafenib	STIVARGA
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
talazoparib	TALZENNA
talimogene laherparepvec	IMLYGIC
tazemetostat	TAZVERIK
tisagenlecleucel	KYMRIAH
trabectedin	YONDELIS
trametinib dimethyl sulfoxide	MEKINIST

trastuzumab-anns	KANJINTI
trastuzumab-dkst	OGIVRI
trastuzumab-dttb	ONTRUZANT
trastuzumab-qyyp	TRAZIMERA
trastuzumab-hyaluronidase-oysk	HERCEPTIN HYLECTA
trifluridine/tipiracil HCl	LONSURF
tucatinib	TUKYSA
vandetanib	CAPRELSA
vandetanib	VANDETANIB
vemurafenib	ZELBORAF
venetoclax	VENCLEXTA
venetoclax	VENCLEXTA STARTING PACK
vismodegib	ERIVEDGE
zanubrutinib	BRUKINSA
ziv-aflibercept	ZALTRAP

P&T/DUR Review: 6/2020 (JP)
Implementation: 10/1/20

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

Date of Review: December 2020

Date of Last Review: November 2019
Literature Search: 06/20/19 – 8/14/20

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

Conclusions:

- Since the last class update on drugs used to manage substance use disorders (SUDs), 3 new systematic reviews[1-3] were published and 2 guidelines were updated.[4,5]
- A moderate-quality 2019 systematic review and meta-analyses aimed to ascertain whether varenicline improves drinking-related outcomes in subjects with alcohol use disorders (AUDs).[1] In the meta-analyses, no significant differences in percentage of heavy drinking days (weighted mean difference [WMD] = -1.09; 95% confidence interval [CI], -4.86 to 2.69), number of drinks per drinking day (WMD = -0.71; 95% CI, -1.44 to 0.03), or percentage of days abstinent (WMD=3.89; 95% CI,-1.25 to 9.02) were noted varenicline 2 mg once daily.[1] A statistically significant decrease in craving was observed (n=436; standard mean difference [SMD] = -0.63; 95% CI,-1.18 to -0.08).[1] In this systematic review and meta-analyses, varenicline was shown to reduce alcohol craving but not improve drinking-related outcomes in subjects with AUDs.[1]
- A systematic review funded by United States (U.S.) Department of Veterans Affairs (VA) in 2020 reviewed the benefits and risks for the treatment of cannabis use disorder (CUD).[2] Overall, there is limited evidence due to the small number of studies investigating most drug classes, small sample sizes, high attrition rates, and other methodological flaws in nearly half the trials.[2] Low- to moderate-strength evidence shows that buspirone, cannabinoids, and SSRIs are ineffective for decreasing cannabis use or improving abstinence.[2] Insufficient evidence was available to draw conclusions about the effectiveness of managing CUD for other drug classes including mood stabilizers, antipsychotics, and anticonvulsants.[2]
- In May 2020, the Agency for Healthcare Research and Quality (AHRQ) published a systematic review evaluating behavioral, pharmacologic and combined interventions for adolescents aged 12 to 20 years with problematic SUD.[3] Motivational interviewing (MI) reduced heavy alcohol use days by 0.7 days/month (low strength of evidence [SoE], alcohol use days by 1.2 days/month (moderate SoE), and overall substance use problems with a SMD of 0.5 days (low SoE), compared with treatment as usual.[3] Brief MI did not reduce cannabis use days (net mean difference of 0; moderate SoE).[3] Across multiple intensive interventions, family focused therapy was most effective, reducing alcohol use days by 3.5 days/month compared with treatment as usual (low SoE).[3] No intensive interventions reduced cannabis use days (low SoE).[3] Pharmacologic treatment of OUD led to a more than 4 times greater likelihood of abstinence with extended courses (2 to 3 months) of buprenorphine compared to short courses (14 to 28 days; low SoE).[3]
- In January 2020, the Substance Abuse and Mental Health Services Administration (SAMHSA) published an updated treatment protocol focused on medications for opioid use disorder (OUD).[4] Pertinent recommendations include: updating the expanded list of "other qualifying practitioners" who are eligible to apply for a waiver to prescribe buprenorphine; clarifying that buprenorphine is available in an extended-release injection and subdermal formulations; and adding information about possible clinical interactions between formulations of buprenorphine, naltrexone, and other medications.[4]

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- In June 2020, the U.S. Preventative Services Task Force (USPSTF) updated its 2008 recommendations for screening for unhealthy drug use in adults and adolescents.[5] This recommendation statement applies to adults 18 years or older, including pregnant and postpartum persons, and adolescents aged 12 to 17 years in primary care settings.[5] In adults, the USPSTF concludes with moderate certainty that screening by asking questions about unhealthy drug use has moderate net benefit when services for accurate diagnosis of unhealthy drug use or drug use disorders, effective treatment, and appropriate care can be offered or referred.[5] In adolescents, because of the lack of evidence, the USPSTF concludes that the benefits and harms of screening for unhealthy drug use are uncertain and that the balance of benefits and harms cannot be determined.[5] The USPSTF recommends screening by asking questions about unhealthy drug use in adults 18 years or older.[5]

Recommendations:

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

Summary of Prior Reviews and Current Policy

In January 2017, the Pharmacy & Therapeutics (P and T) Committee recommended removal of PA criteria for naltrexone extended-release injection and preferred buprenorphine/naloxone sublingual tablets and film (unless the daily dose of buprenorphine exceeds 24 mg) in order to minimize barriers to care and provide increased access to medications for the treatment of SUD. At the January 2019 P & T Committee meeting, a policy evaluation assessing the impact of removing PA requirements for preferred medication assisted-treatments (MAT) for management of OUD was presented. It was reported that utilization of buprenorphine/naloxone and medical claims for MAT continue to increase. After removal of the PA criteria in January 2017, approximately 83% of patients prescribed MAT had an initial paid claim compared to 40% of patients in the year prior to the PA removal.

In January 2019, a class update focused on drugs used to manage SUDs was presented to the P & T Committee. At that meeting, lofexidine (Lucemyra™) tablets and extended-release subcutaneous buprenorphine injection (Sublocade™) were designated as non-preferred on the PDL and PA criteria were implemented to ensure appropriate utilization.

At the November 2019 P and T meeting, buprenorphine sublingual tablets, disulfiram tablets, and buprenorphine/naloxone film (Bunavail®) were designated as voluntary non-preferred, while buprenorphine injection (Sublocade®) was designated as preferred on the PDL after reviewing costs in executive session. The recommendation was made to designate new products in this class as voluntary non-preferred due to legislation designed to ensure open access to SUD treatments. **Appendix 1** lists the current PDL status for medications used in treatment of SUD. Buprenorphine monotherapy and buprenorphine/naloxone products exceeding 24 mg per day and lofexidine require PA as outlined in the clinical PA criteria listed in **Appendix 4**. In the second quarter of 2020 (May through September 2020), most of the OHP FFS pharmacy claims for SUD medications were for oral buprenorphine/naloxone (1,300 claims), followed by oral buprenorphine (334 claims), oral naltrexone (209 claims), extended-release subcutaneous buprenorphine injection (21 claims) and extended-release naltrexone injection (10 claims). Similar trends were observed in the second quarter of 2019. In the first quarter of 2020 (January through April) there were approximately 3500 physician administered claims for oral buprenorphine/naloxone (2,449 claims), extended-release naltrexone injection (11 claims) and oral buprenorphine (978 claims). Physician administered claims include physician offices and SUD clinics.

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 literature scan is available in **Appendix 3**, which includes dates, search terms and

limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

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

New Systematic Reviews:

The Impact of Varenicline on Alcohol Consumption in Subjects with Alcohol Use Disorders

A moderate-quality 2019 systematic review and meta-analyses aimed to ascertain whether varenicline improves drinking-related outcomes in subjects with AUDs.[1] Literature was searched through August 2019 for randomized, placebo-controlled trials in humans.[1] Although varenicline has been shown to be safe and effective in improving abstinence in tobacco smokers, results from trials using varenicline for AUDs are inconsistent.[1] Ten randomized, placebo-controlled studies (n=731, 66.6% male, 55.1% smokers) that examined studies of subjects with heavy drinking or alcohol dependence/AUD and reported alcohol use-related outcomes met inclusion critieria.[1] Overall risk of bias was low for all 10 RCTs.[1] The primary outcome of interest was percentage of heavy drinking days.[1] Secondary outcomes included the number of drinks per drinking day, percentage of days abstinent, and change in alcohol craving.[1]

In the meta-analyses, no significant differences in percentage of heavy drinking days (n=597; WMD =-1.09; 95% CI, -4.86 to 2.69; I^2=22%), number of drinks per drinking day (n=570; WMD = -0.71; 95% CI, -1.44 to 0.03; I^2=0%), or percentage of days abstinent (n=439; WMD=3.89; 95% CI, -1.25 to 9.02; I^2=0%) were noted with varenicline 2 mg once daily.[1] A statistically significant decrease in craving was observed (n=436; SMD = -0.63; 95% CI, -1.18 to -0.08; I^2=84%).[1] In summary, varenicline was shown to reduce alcohol craving but not improve drinking-related outcomes in subjects with AUDs.[1]

Pharmacotherapy for the Treatment of Cannabis Use Disorder

A systematic review funded by the VA in 2020 reviewed the benefits and risks for the treatment of CUD.[2] Literature was searched from January 2014 through September 2019.[2] Fourteen new RCTs and 12 RCTs from a previous 2014 Cochrane review met inclusion criteria.[2] Because populations, duration, and concurrent interventions were heterogeneous among studies, the authors did not pool their findings, nor did they pool data across drug classes.[2] Overall, the evidence base is limited because of the small number of studies investigating most drug classes, small sample sizes, nearly universal high attrition rates, and other methodological flaws in approximately half of the trials.[2]

Four trials with low risk of bias (ROB) and 2 high-ROB trials evaluated the use of antidepressants (escitalopram, fluoxetine, bupropion, nefazodone, venlafaxine, and vilazodone) to treat CUD.[2] Overall, low-strength evidence showed that selective serotonin reuptake inhibitors (SSRIs) did not reduce cannabis use (as assessed by negative urinalysis results) and that neither SSRIs nor bupropion improved treatment adherence.[2] Most studies had high rates of attrition (as high as 60%), which increased risk of bias in these trials.[2]

The authors found insufficient evidence for the effectiveness of antipsychotics in treating CUD.[2] One high-ROB head-to-head RCT compared ziprasidone and clozapine (n=30) in adults with CUD and a psychotic spectrum disorder. Findings indicated no difference between groups in cannabis use changes or treatment adherence.[2] Results suggest that clozapine may be associated with more adverse events and that ziprasidone may be associated with better drug tolerance and psychotherapy adherence.[2]

Low-strength evidence from 1 low-ROB and 1 unclear-ROB RCT showed that buspirone has no benefit over placebo for treatment retention (calculated risk ratio, 0.92 [95% CI, 0.61 to 1.26]).[2] Two RCTs with mood stabilizers; 1 with low ROB (lithium) and the other with high ROB (divalproex), provide insufficient evidence from which to form conclusions about their respective efficacy in CUD treatment.[2] Theses trials found no difference between divalproex or lithium and placebo in cannabis abstinence, changes in frequency or quantity of cannabis use, or treatment adherence.[2] Regarding withdrawal symptoms, divalproex did not differ from placebo in craving or irritability.[2] Lithium and placebo were similar in reported withdrawal severity.[2] However, lithium was more effective for attenuating nightmares, loss of appetite, and stomach aches.[2]

Three low-ROB RCTs and 3 RCTs with unclear ROB examined the use of cannabinoids (nabilone, dronabinol, and nabiximol) in treating CUD.[2] Dronabinol is FDA-approved for treatment of adults with anorexia associated with Acquired Immunodeficiency Syndrome (AIDS) or for nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond to conventional antiemetic treatments.[6] Nabilone is FDA-approved for treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.[7] Nabiximol is an investigational product containing tetrahydrocannabinol (THC) and cannabidiol (CBD) that is not FDA-approved. It is available as an oral spray in the European Union for the treatment of spasticity due to multiple sclerosis.[8] One small RCT (n=18) comparing nabilone with placebo found no difference in any outcome of interest.[2] Two other trials, 1 comparing dronabinol and the other comparing a combination of dronabinol and lofexidine with placebo, found no difference in the achievement of abstinence, reduction in cannabis use, cannabis craving, or harms.[2] Findings were mixed for the effect of dronabinol on withdrawal symptoms and treatment retention.[2]

Two small RCTs with unclear ROB provide insufficient evidence about the effects of gabapentin and topiramate on all outcomes of interest because of small sample sizes, high attrition, and methodological issues.[2] Participants receiving gabapentin (n=50), but not those receiving topiramate (n=66), substantially decreased their cannabis use compared with those receiving placebo.[2] In addition, gabapentin was associated with a decrease in depressive symptoms, better neurocognitive performance, and treatment retention and was more effective than placebo in mitigating withdrawal symptoms.[2] Participants receiving topiramate had poorer depressive and neurocognitive outcomes and higher rates of attrition than those receiving placebo.[2]

In summary, this systematic review examined 26 trials of pharmacotherapies to treat CUD. Low- to moderate-strength evidence shows that buspirone, cannabinoids, and SSRIs are ineffective for decreasing cannabis use or improving abstinence.[2] Insufficient evidence is available to draw conclusions about the effectiveness of other drug classes in managing CUD including mood stabilizers, antipsychotics, and anticonvulsants.[2]

<u>Interventions for Substance Use Disorders in Adolescents</u>

In May 2020, AHRQ published a systematic review evaluating behavioral, pharmacologic and combined interventions for adolescents aged 12 to 20 years with problematic SUD.[3] The literature search was conducted through November 2019.[3] One hundred eighteen studies met inclusion criteria.[3] Most studies enrolled adolescents with some combination of alcohol and cannabis use.[3] The most commonly reported outcomes included frequency of use and abstinence.[3] Very few studies evaluated users of opioids, methamphetamines, or substances other than alcohol or cannabis.[3] Studies often combined different types of interventions, making comparisons of specific interventions difficult.[3] The available studies did not consistently report a common set of outcomes, which limited the ability to combine information from potentially relevant studies.[3] For most outcomes, individual studies were deemed to have moderate risk of bias, most commonly due to incomplete outcome data, poor compliance, and a lack of blinding of participants, study personnel, and outcome assessors.[3]

Motivational interviewing reduced heavy alcohol use days by 0.7 days/month (low SoE, alcohol use days by 1.2 days/month (moderate SoE), and overall substance use problems with a SMD of 0.5 days (low SoE), compared with treatment as usual.[3] Brief MI did not reduce cannabis use days (net mean difference of 0; moderate SoE).[3] Across multiple intensive interventions, family focused therapy was most effective, reducing alcohol use days by 3.5 days/month compared with treatment as usual (low SoE).[3] No intensive interventions reduced cannabis use days (low SoE).[3] Pharmacologic treatment of OUD led to a more than 4 times greater likelihood of abstinence with extended courses (2 to 3 months) of buprenorphine compared to short courses (14 to 28 days; low SoE).[3] More research is needed to understand the role of medications in treatment of alcohol and cannabis use disorders and of pharmacological treatments typically used for comorbid psychiatric illnesses.[3]

After review, 10 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[9-18]

New Guidelines:

High Quality Guidelines:

Medications for Opioid Use Disorder

In January 2020, SAMHSA published an updated Treatment Improvement Protocol focused on medications for OUD.[4] Improving access is crucial to closing the wide gap between the need for treatment with OUD medications and the availability of such treatment, given the strong evidence of OUD medications' effectiveness.[4] Pertinent changes to the protocol include:

- Updating the expanded list of "other qualifying practitioners" who are eligible to apply for a waiver to prescribe buprenorphine (i.e., clinical nurse specialists, certified registered nurse anesthetists, and certified nurse midwives).[4]
- Clarifying that buprenorphine is available in an extended-release injection formulation.[4]
- Adding information about the use of subdermal formulations of buprenorphine (i.e., Probuphine and Sublocade).[4]
- Adding information about possible clinical interactions between formulations of buprenorphine and naltrexone with various other medications and products.[4]
- Improving the language to make clear the importance of testing for HIV and hepatitis C.[4]
- Updating recommendations from the USPSTF on performing drug screening for adults in primary care settings.[4]

Of note, prior to the COVID-19 pandemic, an in-person evaluation was required to initiate treatment with buprenorphine or methadone and daily visits were often required to pick up methadone doses. While an in-person evaluation is still required to initiate methadone treatment, the Drug Enforcement Agency (DEA) and SAMHSA are allowing buprenorphine to be prescribed via telehealth or over the phone.[19] For both medications, the temporary SAMHSA guidelines allow treatment centers and programs to dispense up to 28 doses for clinically stable patients and up to 14 doses for less clinically stable patients.[19]

Screening for Unhealthy Drug Use

In June 2020, the USPSTF updated its 2008 recommendations for screening for unhealthy drug use in adults and adolescents.[5] Screening refers to asking questions about unhealthy drug use, not testing biological specimens. This recommendation statement applies to adults 18 years or older, including pregnant and postpartum persons, and adolescents aged 12 to 17 years in primary care settings.[5] This statement does not apply to adolescents or adults who have a currently diagnosed drug use disorder or are currently undergoing or have been referred for drug use treatment.[5] This statement applies to settings and populations for which services for accurate diagnosis, effective treatment, and appropriate care can be offered or referred.[5] In adults, the USPSTF concludes with moderate

certainty that screening by asking questions about unhealthy drug use has moderate net benefit when services for accurate diagnosis of unhealthy drug use or drug use disorders, effective treatment, and appropriate care can be offered or referred.[5] In adolescents, because of the lack of evidence, the USPSTF concludes that the benefits and harms of screening for unhealthy drug use are uncertain and that the balance of benefits and harms cannot be determined.[5] The USPSTF recommends screening by asking questions about unhealthy drug use in adults 18 years or older.[5] Screening should be implemented when services for accurate diagnosis, effective treatment, and appropriate care can be offered or referred (B recommendation).[5]

Additional Guidelines for Clinical Context:

Primary Care-Based Interventions to Prevent Illicit Drug Use in Children, Adolescents, and Young Adults

Illicit drug use is associated with many negative health, social, and economic consequences and is a significant contributor to 3 of the leading causes of death among young persons (aged 10-24 years): unintentional injuries including motor vehicle crashes, suicide, and homicide.[20] To update its 2014 recommendation, the USPSTF commissioned a 2020 review of the evidence on the potential benefits and harms of interventions to prevent illicit drug use in children, adolescents, and young adults.[20] This recommendation applies to children (11 years and younger), adolescents (aged 12-17 years), and young adults (aged 18-25 years), including pregnant persons.[20] Only 1 study reported on harms and 2 studies reported an increase in illicit drug use after drug prevention interventions.[20] Because of limited and inadequate evidence. The USPSTF concludes that the benefits and harms of primary care-based interventions to prevent illicit drug use in children, adolescents, and young adults are uncertain, that the evidence is insufficient to assess the balance of benefits and harms, and that more research is needed (Class I Statement).[20]

After review, 1 guideline was excluded due to poor quality.[21]

New Formulations: No new formulations have been marketed since the last review.

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)
Naloxone	Narcan	July 2020	Drug Safety Communication[22]	For all patients who are prescribed opioid pain relievers, health care professionals should discuss the availability of naloxone, and consider prescribing it to patients who are at increased risk of opioid overdose. Such patients include those who are using concomitant benzodiazepines or other medicines that depress the central nervous system, who have a history of OUD, or who have experienced a previous opioid overdose. Health care professionals should also consider prescribing naloxone if the patient has household members, including children, or other close contacts who are at risk for accidental ingestion or opioid overdose.

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Appendix 1: Current Preferred Drug List

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

Appendix 2: New Comparative Clinical Trials

A total of 102 citations were manually reviewed from the initial literature search. After further review, 102 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).

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to August Week 1 2020 and Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 August 14, 2020

1 acamprosate.mp.	809
2 exp Disulfiram/	951
3 exp Naltrexone/	5107
4 exp Alcoholism/	32020
5 exp Substance-Related Disorders/	165191
6 exp Alcohol Deterrents/	6593
7 Buprenorphine	4081
8 Buprenorphine, Naloxone Drug combination	281
9. lofexidine	120
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	170861

10 limit 9 to (English language and humans and yr="2019-Current" and (clinical trial, all or clinical trial or comparative study or controlled clinical trial or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 102

Buprenorphine and Buprenorphine/Naloxone

Goals:

- Prevent use of high-dose transmucosal buprenorphine products for off-label indications.

Length of Authorization:

- Up to 6 months

Requires PA:

- Transmucosal buprenorphine products that exceed an average daily dose of 24 mg per day

Covered Alternatives:

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

Approval Criteria		
1. Is the diagnosis funded by the OHP?	**Yes:** Go to #2	**No:** Pass to RPh. Deny; not funded by OHP
2. Is the prescription for opioid use disorder (opioid dependence or addiction)?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the prescription for a transmucosal formulation of buprenorphine (film, tablet) with an average daily dose of more than 24 mg (e.g., >24 mg/day or >48 mg every other day)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #4

Approval Criteria		
4. Is the requested medication a preferred agent?	**Yes:** Approve for anticipated length of treatment or 6 months, whichever is less. Note: Notify prescriber concomitant naloxone is recommended if not present in claims history.	**No:** Go to #5
5. Will the prescriber switch to a preferred product? Note: Preferred products are reviewed for comparative safety and efficacy by the Oregon Pharmacy and Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Approve for anticipated length of treatment or 6 months, whichever is less. Note: Notify prescriber concomitant naloxone is recommended if not present in claims history.

P&T/DUR Review: *12/20 (DM); 11/19 (DM); 1/19; 1/17; 9/16; 1/15; 9/09; 5/09*
Implementation: *1/1/2020; 3/1/2019; 4/1/2017; 9/1/13; 1/1/10*

Lofexidine

Goal(s):
- Encourage use of substance use disorder medications on the Preferred Drug List.
- Restrict use of lofexidine under this PA to ensure medically appropriate use of lofexidine based on FDA-approved indications.

Length of Authorization:
- Up to 14 days

Requires PA:
- Lofexidine 0.18mg tablets

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication? (Mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults)	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a PA. Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Approve for up to 14 days of total therapy. Note: FDA approved indication is for up to 14 days of therapy AND Notify prescriber concomitant naloxone is recommended if not present in claims history.

P&T/DUR Review: 12/20 (DM); 11/19 (DM); 1/19
Implementation: 3/1/19

Drug Use Research & Management Program
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Salem, Oregon 97301-1079
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Drug Class Literature Scan: Newer Antiemetics

Date of Review: December 2020

Date of Last Review: September 2017
Literature Search: 07/01/17 – 10/09/20

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

Conclusions:

- There is one guideline, 2 systematic reviews, 2 new indications, 2 new formulations and 2 safety alerts providing evidence for this review. The evidence contributing to this review supports current antiemetic policy or lacks the quality of evidence to institute changes to the current preferred drug list (PDL).
- The National Institute for Health and Care Excellence (NICE) found evidence that doxylamine/pyridoxine was effective for improving Pregnancy Unique Quantification of Emesis (PUQE) scores. NICE recommends the use of doxylamine/pyridoxine for use in patients who prefer a licensed product for use in pregnancy.[1]
- A 2020 report by the Canadian Agency for Drugs and Technology in Health (CADTH) found ondansetron, when studied in pediatric patients with mild to moderate dehydration due to gastroenteritis, to decrease the need for intravenous (IV) rehydration and reduced the incidence of vomiting compared to placebo.[2]
- Updated 2020 National Comprehensive Cancer Network (NCCN) guidelines for antiemesis in cancer supports current policy.[1]

New Products/Formulations

- BARHEMSYS (amisulpride) is a is a dopamine-2 antagonist approved for the prevention and treatment of postoperative nausea and vomiting (PONV), either alone or in combination with an antiemetic of a different class in adult patients. A complete response was seen in patients when treated with amisulpride for prophylaxis (number needed to treat [NNT] 8-9) and for treatment (NNT 8-10), both used as a single dose treatment within 24 hours of surgical procedure. Amisulpride offers a treatment option for patients not responding, or who cannot tolerate, current standard of care therapies for PONV (e.g., serotonin [5-HT3] receptor antagonists [RAs]).[3]
- CINVANTI (aprepitant) is a new formulation of injectable aprepitant 130 mg that was approved in October of 2019.[4] Aprepitant is approved as preventative therapy for acute and delayed nausea and vomiting associated with initial and repeat courses of medium emetogenic chemotherapy (MEC) and high emetogenic chemotherapy (HEC) regimens.
- EMEND (fosaprepitant) was approved for the use in pediatric patients 6 months of age and older for prevention of chemotherapy-induced nausea and vomiting (CINV).[5]
- Palonosetron – An expanded indication for palonosetron was approved in 2018 for patients 1 month to less than 17 years of age for the prevention of acute nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy.[6]

Author: Kathy Sentena, PharmD

Recommendations:

- There is no new clinical evidence to warrant changes to the preferred drug list (PDL).
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy

- A literature review of the clinical efficacy and safety of the antiemetic class in September of 2017 resulted in no changes to the PDL and after executive session there were also no changes to the PDL.
- Evidence recommends the use of the newer antiemetics (5-HT3 RAs, neurokinin 1 receptor antagonists [NK1 RAs]), in addition to drugs from other classes (e.g., olanzapine, dexamethasone, and benzodiazepines) for chemotherapy-induced and radiation-induced nausea and vomiting.
- The 5-HT3 RAs have been shown to have similar efficacy when studied at recommended doses and dosing intervals for chemotherapy induced nausea/vomiting.
- There is no evidence to suggest clinically significant differences between the newer antiemetics used for PONV.

- Current policy has ondansetron tablets, rapid tablets and solution as preferred therapies on the Oregon Health Plan (OHP) fee-for-service (FFS) PDL. Almost all claims are for preferred products (98%) and overall quarterly costs for the class are not substantial. Non-preferred products are subject to clinical PA criteria (**Appendix 5**).

Methods:

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

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

New Systematic Reviews:

<u>NICE – Doxylamine/Pyridoxine for Treating Nausea and Vomiting of Pregnancy</u>

An evidence review for the use of doxylamine 10 mg/pyridoxine 10 mg in pregnant women with nausea and vomiting was conducted by NICE in 2019.[7] A literature search retrieved 2 randomized controlled trials available for analysis. There was evidence of improvement in symptoms of nausea and vomiting as demonstrated by the PUQE. The PUQE is a questionnaire consisting of 3 questions with scores ranging from 3-15. Higher scores indicate more severe nausea/vomiting, but no minimal clinically important difference has been reported.[7] Patients in the doxylamine/pyridoxine group demonstrated a reduction of -

4.8 in PUQE score compared to -3.9 for placebo (p=0.006).[7] A second study originally done in 1975, and published in 2017, substantiated results of the more recent study.

Recommendations from NICE, via the Royal College of Obstetricians and Gynecologists (RCOG), for the treatment of pregnancy related nausea and vomiting are as follows:

- First line: Antihistamines and phenothiazines
- Second line: metoclopramide, domperidone (not available in the United States [US]) or ondansetron
- Third line: corticosteroids

RCOG recommendations precede the approval of doxylamine/pyridoxine, and it can be recommended for patients who prefer a licensed antiemetic product for use in pregnancy.[7] Older therapies are not specifically approved for use in pregnancy but are the clinical standard in managing nausea and vomiting in this population.

There is only limited evidence on the topic, with short study periods (15 days) and use of a subjective, patient-reported outcome measure (e.g., PUQE). There are no active treatment comparison trials.

<u>CADTH – Ondansetron and Oral Rehydration Therapy in Pediatric Patients with Dehydration: A Review of Clinical Effectiveness</u>

A 2020 CADTH rapid response report evaluated the evidence for the efficacy of ondansetron, alone or in combination with oral rehydration, compared to oral rehydration alone in pediatric patients at risk of mild to moderate dehydration.[2] A literature search ranging from January 2015 to January 2020 identified 6 trials that met criteria for inclusion; 5 randomized clinical trials and 1 non-randomized retrospective comparative cohort study. All studies were conducted at sites other than the United States (US) with the exception of the non-randomized study.

Low strength of evidence found ondansetron to decrease the need for IV rehydration and reduce the incidence of vomiting compared to placebo, in pediatric patients with mild to moderate dehydration due to gastroenteritis (meta-analysis was not performed).[2] One trial found that ondansetron was not superior to placebo for reduction in vomiting. Non-randomized trial findings showed ondansetron to have no effect on emergency department readmissions within 72 hours, compared to no treatment.

After review, 14 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[8–21]

New Guidelines:

High Quality Guidelines:

<u>NCCN – Anitemesis</u>

The NCCN is a high-quality guideline which updates recommendations for antiemetic use in oncology on an annual basis.[1] Guidance recommendations are based on a NCCN categories of evidence and consensus (**Table 1**). All recommendations in the guideline are considered category 2A unless specifically noted otherwise.

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

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

Chemotherapy related nausea/vomiting is referred to as CINV. Antiemetic therapies are categorized as: acute, delayed, anticipatory, breakthrough or refractory. The emetogenic potential of the chemotherapy or radiation regimen dictates the appropriate antiemetic therapy. Risk categories are as follows: high, moderate, low and minimal.[1] It is recommended that antiemetic therapies be initiated before treatment with anticancer therapies. Evidence demonstrates that antiemetics are equally effective and individual antiemetic selection should be based on drug-drug interactions, patient-specific factors and individual experience. Selection of antiemetic regimen should always be based on the drug with the highest emetic risk. Antiemetic treatment recommendations for parenteral anticancer therapies are provided in **Tables 2, 3 and 4**.[1] Parenteral anticancer therapies with minimal emetic potential require no routine prophylaxis.

Table 2. NCCN Recommendations for Acute and Delayed Emesis Prevention for High Emetic Risk Parenteral Anticancer Agents*†[1]

Day 1 (Select option A, B or C)	Days 2, 3, 4
Treatment option A (preferred) use the following combination: • Olanzapine orally once • NK1 RA once (PO or IV) • 5-HT3 RA once (PO, SQ or IV) • Dexamethasone once (PO or IV)	Treatment option A: • Olanzapine orally on days 2, 3 and 4 • Aprepitant 80 mg orally on days 2, 3 (if aprepitant orally was used on day 1) • Dexamethasone daily on days 2, 3, 4 (PO/IV)
Treatment option B, use the following combination: • Olanzapine orally once • Palonosetron once (IV) • Dexamethasone once (PO/IV)	Treatment option B: • Olanzapine orally daily on days 2, 3, 4
Treatment option C, use the following combination: • NK1 RA once (PO or IV) • 5-HT3 RA once (PO, SQ or IV) • Dexamethasone once (PO/IV)	Treatment option C: • Aprepitant 80 mg orally on days 2, 3 (if aprepitant PO was used on day 1) • Dexamethasone daily on days 2, 3, 4 (PO/IV)
Abbreviations: 5-HT3 RA – serotonin receptor antagonist; IV – intravenous; NK1 RA – neurokinin-1 receptor antagonist; PO – by mouth; SQ – subcutaneous Key: * All treatments should be started before chemotherapy; † With or without oral lorazepam, IV or sublingual every 6 hours as needed for days 1-4, with or without H2 blocker or proton pump inhibitor. For regimens containing olanzapine, only use oral lorazepam if needed.	

Table 3. NCCN Recommendations for Acute and Delayed Emesis Prevention for Moderate Emetic Risk Parenteral Anticancer Agents*†[1]

Day 1 (Select option D, E, or F)	Days 2, 3
Treatment option D (preferred) use the following combination: • 5-HT3 RA (PO, SQ, IV) • Dexamethasone once (PO or IV)	Treatment option D: • Dexamethasone daily on days 2, 3 (PO/IV) **OR** • 5-HT3 RA monotherapy daily on days 2, 3

Treatment option E, use the following combination: • Olanzapine orally once • Palonosetron IV once • Dexamethasone once (PO/IV)	Treatment option E: • Olanzapine orally daily on days 2, 3
Treatment option F, use the following combination: • NK1 RA once (PO or IV) • 5-HT3 RA once (PO, SQ or IV) • Dexamethasone once (PO/IV)	Treatment option F: • Aprepitant 80 mg orally on days 2, 3 (if aprepitant orally was used on day 1) +/- Dexamethasone days 2,3 (PO/IV)
Abbreviations: 5-HT3 RA – serotonin receptor antagonist; IV – intravenous; NK1 RA – neurokinin-1 receptor antagonist; PO – by mouth; SQ – subcutaneous Key: * All treatments should be started before chemotherapy; † With or without lorazepam PO, IV or sublingual every 6 hours as needed for days 1-4. With or without H2 blocker or proton pump inhibitor. For regimens containing olanzapine, only use PO lorazepam if needed.	

Table 4. NCCN Recommendations for Acute and Delayed Emesis Prevention for Low Emetic Risk Parenteral Anticancer Agents*†[1]

Repeat daily for multiday doses of chemotherapy
• Dexamethasone once (PO or IV) once OR • Metoclopramide (PO/IV) once OR • Prochlorperazine (PO/IV) once OR • 5-HT3 RA (PO) once
Abbreviations: 5-HT3 RA – serotonin receptor antagonist; IV – intravenous; PO – by mouth; SQ – subcutaneous Key: * All treatments should be started before chemotherapy; † With or without oral lorazepam, IV or sublingual every 6 hours as needed for days 1-4

Oral chemotherapy can have a risk of emesis, and recommendations for antiemetics are separated into high to moderate emetic risk and low to minimal emetic risk (**Table 5**).

Table 5. NCCN Recommendations for Oral Chemotherapy Emesis Prevention*[1]

High to Moderate Emetic Risk	• Start before chemotherapy and continue daily while receiving chemotherapy • 5-HT3 RA recommended (PO or transdermal)
Low to Minimal Emetic Risk	• As-needed antiemetic use is recommended • If nausea or vomiting occurs, start treatment before chemotherapy in future cycles and continue daily • Use metoclopramide orally OR • Prochlorperazine orally OR • 5-HT3 RA orally
Abbreviations: 5-HT3 RA – serotonin receptor antagonist; PO - orally Key: *With or without oral lorazepam, IV or sublingual every 6 hours as needed	

In addition to scheduled emesis prevention, breakthrough treatment for chemotherapy-induced nausea and vomiting may be needed.[1] In general, breakthrough treatment should be from a different drug class than currently used therapy and should be added to current regimen (see options below).[1] If nausea and vomiting is controlled, the medication should be continued on a schedule. If breakthrough nausea/vomiting remains uncontrolled then a dose adjustment should be considered and/or one therapy from another drug class should be added.[1] Re-evaluation of antiemetic therapy should be considered to prevent need for breakthrough therapy and a higher level of primary antiemetic treatment should be used for the next cycle.

Antiemetic choices for breakthrough chemotherapy-induced nausea/vomiting are the following:

- Olanzapine orally (preferred category 1)
- Benzodiazepine orally/sublingual/IV
- Cannabinoid orally
- Haloperidol orally/IV
- Metoclopramide orally/IV
- Scopolamine transdermal patch
- Phenothiazine (prochlorperazine or promethazine)
- 5-HT3 RA orally/transdermal
- Dexamethasone orally/IV

Radiation therapy may also cause nausea/vomiting. Antiemetic therapy for radiation is based on amount of the body that is being irradiated. The use of granisetron orally or ondansetron (+/- dexamethasone orally) should be given to patients as pretreatment for each day patients receive radiation therapy to the upper abdomen/localized sites.[1] For patients receiving total body irradiation, pretreatment for each day of radiation therapy should be with granisetron or ondansetron orally (+/- dexamethasone orally).[1] If the patients is receiving chemotherapy and radiation therapy then recommendations should be based on emetogenicity of chemotherapy regimen.

In patients who experience anticipatory nausea/vomiting, preventative therapy is most important. Recommendations include using optimal antiemetic therapy during every cycle of treatment, avoidance of smells that precipitate treatment, behavioral therapy, acupuncture/acupressure and consideration of anxiolytic therapy.

If patients are receiving multiday emetogenic chemotherapy they may need antiemetic therapy for acute and delayed nausea/vomiting. General therapies include dexamethasone (unless regimen already includes a steroid or olanzapine if the patient can't tolerate dexamethasone), 5-HT3 RAs, and neurokinin-1 receptor antagonists.

After review, one guideline was excluded due to poor quality.[22]

New Formulations/Indications:

CINVANTI (aprepitant) – A new formulation of injectable aprepitant 130 mg was approved in October of 2019.[4] Aprepitant is approved as preventative therapy for the following patients:

- Acute and delayed nausea and vomiting associated with initial and repeat courses of HEC including high-dose cisplatin as a single-dose regimen
- Delayed nausea and vomiting associated with initial and repeat courses of MEC as a single-dose regimen
- Nausea and vomiting associated with initial and repeat courses of MEC as a 3-day regimen

Cinvanti can be given as an intravenous injection over 2 minutes or as an infusion over 30 minutes, to be completed approximately 30 minutes prior to chemotherapy.

EMEND (fosaprepitant) – Fosaprepitant was approved for the use in pediatric patients 6 months of age and older for prevention of CINV.[5] Fosaprepitant is approved for use, in combination with other antiemetics, for the prevention of acute and delayed nausea and vomiting associated with HEC, including high-dose cisplatin, and for delayed nausea and vomiting associated with initial and repeat courses of MEC. Evidence for the pediatric indication was based off of trials in adults with additional safety, efficacy (3-day oral aprepitant trial completed in pediatrics) and pharmacokinetic data.

Aprepitant - In September of 2019, the indication for the use of aprepitant for the prevention of PONV was removed.[23] Use of aprepitant in studies at non-recommended doses and in patients not using the medication for CINV demonstrated a single case of the following adverse events: angioedema and urticaria, constipation, and sub-ileus. Aprepitant is indicated for use only in patients with CINV.

Palonosetron – Palonosetron received an expanded indication for the use in pediatric patients in December of 2018.[6] The use of palonosetron injection has been approved for use in patients 1 month to less than 17 years of age for the prevention of acute nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including HEC. A study supporting the indication evaluated 165 pediatric patients given palonosetron 20 mcg/kg (max dose of 1.5 mg) 30 minutes prior to start of chemotherapy.

New FDA Safety Alerts:

Table 5. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Rolapitant[25]	VARUBI	August 2020	Contraindications	Use in pediatric patients less than 2 years of age is contraindicated due to irreversible impairment of sexual development and fertility in juvenile rats.
Fosaprepitant[5]	EMEND	February 2018	Warnings and Precautions	Infusion site reactions (including thrombophlebitis, necrosis, and vasculitis) have occurred. A majority or reactions have been in patients receiving vesicant chemotherapy. Avoid infusion in to small veins. Medication should be discontinued and appropriate treatment administered if severe reaction occurs.

Abbreviated New Drug Review:

Trade Name: Amisulpride (BARHEMSYS)
Indications
• Prevention of PONV, either alone or in combination with an antiemetic of a different class in adult patients.[3] • Treatment of PONV in patients who have received antiemetic prophylaxis with an agent of a different class or have not received prophylaxis in adult patients.[3]
Dosage
• Prevention of PONV (alone or in combination): 5 mg as a single intravenous dose (IV) infused over 1 to 2 minutes at the time of induction of anesthesia.[3] • Treatment of PONV: 10 mg as a single IV dose infused over 1 to 2 minutes in the event of nausea and/or vomiting after a surgical procedure.[3]
Background
Amisulpride is a dopamine-2 antagonist used for prophylaxis and treatment of PONV. First-line treatments recommended for surgical prophylaxis are $5HT_3$ RAs.[3]
Efficacy
Prophylaxis: Prevention of PONV was studied in 2 double-blind, placebo-controlled, randomized controlled trials in patients scheduled for elective surgery with general anesthesia.[3] Amisulpride was given as monotherapy in the first study in patients with 2-4 risk factors for PONV and as combination therapy in the second study (administered with ondansetron, dexamethasone or betamethasone) in patients with 3-4 risk factors for PONV. The primary endpoint in both studies was a complete response which was defined as absence of any episodes of emesis or use of rescue medication within the first 24 hours after treatment. Results: - Forty-four percent of patients treated with amisulpride had a complete response compared to 33% in the placebo group in the first study (unadjusted mean difference [MD] 12%; 95% CI, 2% to 22%; ARR 11%/NNT 9).[3] - In the second study, 58% of patients had a complete response compared to 47% in the placebo group (MD 13%; 95% CI, 5% to 22%; ARR 13%/NNT 8).[3] Treatment: Amisulpride was studied in two double-bind, placebo-controlled, multi-center, randomized controlled trials in patients with PONV following elective surgery with general anesthesia. The first study was in patients, with 2-3 risk factors for PONV, who had not received any prophylactic treatment for PONV. In the second study, patients with 3-4 risk factors for PONV had been treated and failed therapy with an antiemetic from another class ($5HT_3$ antagonists, dexamethasone or other antiemetic) for PONV for current procedure. A complete response was the primary endpoint in both studies, which was defined as absence of any episodes of emesis or use of rescue medication within the first 24 hours after treatment (excluding emesis within the first 30 minutes). Results: - A complete response was demonstrated in 31% of patients treated with amisulpride in the first study compared to 22% of patients treated with placebo (treatment naïve study) (MD 10%; 95% CI, 1% to 19%; ARR 10%/NNT 10).[3,26] - A complete response was demonstrated in 42% of patients treated with amisulpride in the second study compared to 29% treated with placebo (prior prophylaxis study) (MD 13%; 95% CI, 5% to 22%; ARR 13%/NNT 8).[3]
Safety
The most common adverse events that occurred in 2% or more of patients taking amisulpride for PONV prevention were the following: increased blood prolactin concentrations, chills, hypokalemia, procedural hypotension and abdominal distention. The use of amisulpride for the treatment of PONV was associated with infusion site reactions as the most common adverse reaction.
Evidence Gaps/Limitations
Amisulpride has only be been studied as a single use injection. There is insufficient evidence for additional doses of amisulpride. Amisulpride has not been studied in pediatric patients.
Recommendation
There is moderate strength of evidence that amisulpride is effective for the treatment and prophylaxis of PONV. Amisulpride is a treatment option for patients not responding or who cannot tolerate current standard of care therapies for PONV.
Abbreviations: ARR – absolute risk reduction; CI – confidence interval; IV – intravenous; MD – mean difference; NNT – number needed to treat; PONV – post-op nausea and vomiting

References:

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2. Canadian Agency for Drugs and Technology in Health. Ondansetron and Oral Rehydration Therapy in Pediatric Patients with Dehydration: A Review of Clinical Effectiveness. *CADTH Rapid Response Report*. February 14, 2020. Available at: https://cadth.ca./ondansetron-and-oral-rehydration-therapy-pediatric-patients-dehydration-clinical-effectiveness. Accessed October 14, 2020.
3. Barhemsys (Amisulpride) [prescribing information]. Indianapolis, IN; Acacia Pharma Inc. February 2020.
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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
ondansetron	ONDANSETRON ODT	TAB RAPDIS	PO	Y
ondansetron HCl	ONDANSETRON HCL	SOLUTION	PO	Y
ondansetron HCl	ONDANSETRON HCL	TABLET	PO	Y
ondansetron HCl	ZOFRAN	TABLET	PO	Y
aprepitant	APREPITANT	CAP DS PK	PO	N
aprepitant	EMEND	CAP DS PK	PO	N
aprepitant	APREPITANT	CAPSULE	PO	N
aprepitant	EMEND	CAPSULE	PO	N
aprepitant	EMEND	SUSP RECON	PO	N
dolasetron mesylate	ANZEMET	TABLET	PO	N
doxylamine succinate/vit B6	BONJESTA	TAB IR DR	PO	N
doxylamine succinate/vit B6	DICLEGIS	TABLET DR	PO	N
doxylamine succinate/vit B6	DOXYLAMINE SUCC-PYRIDOXINE HCL	TABLET DR	PO	N
granisetron	SUSTOL	LIQ ER SYR	SQ	N
granisetron	SANCUSO	PATCH TDWK	TD	N
granisetron HCl	GRANISETRON HCL	TABLET	PO	N
netupitant/palonosetron HCl	AKYNZEO	CAPSULE	PO	N

ondansetron	ZUPLENZ	FILM	PO	N
rolapitant HCl	VARUBI	TABLET	PO	N
amisulpride	BARHEMSYS	VIAL	IV	
aprepitant	CINVANTI	VIAL	IV	
fosaprepitant dimeglumine	EMEND	VIAL	IV	
fosaprepitant dimeglumine	FOSAPREPITANT DIMEGLUMINE	VIAL	IV	
fosnetupitant/palonosetron	AKYNZEO	VIAL	IV	
granisetron HCl	GRANISETRON HCL	VIAL	IV	
granisetron HCl/PF	GRANISETRON HCL	VIAL	IV	
ondansetron HCl	ONDANSETRON HCL	VIAL	IV	
ondansetron HCl in 0.9 % NaCl	ONDANSETRON HCL-0.9% NACL	PIGGYBACK	IV	
Ondansetron HCl in D5W	ONDANSETRON HCL-D5W	PIGGYBACK	IV	
ondansetron HCl/PF	ONDANSETRON HCL	AMPUL	IJ	
ondansetron HCl/PF	ONDANSETRON HCL	SYRINGE	IJ	
ondansetron HCl/PF	ONDANSETRON HCL	VIAL	IJ	
palonosetron HCl	PALONOSETRON HCL	SYRINGE	IV	
palonosetron HCl	ALOXI	VIAL	IV	
palonosetron HCl	PALONOSETRON HCL	VIAL	IV	

Appendix 2: New Comparative Clinical Trials

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

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to October 09, 2020
Search Strategy:

#	Searches	Results
1	ondansetron.mp. or Ondansetron/	5125
2	aprepitant.mp. or Aprepitant/	1121
3	dolasetron.mp.	309
4	doxylamine.mp. or Doxylamine/	515
5	granisetron.mp. or Granisetron/	1785
6	netupitant.mp.	152
7	rolapitant.mp.	90
8	amisulpride.mp. or Amisulpride/	1357
9	fosaprepitant.mp.	174
10	palonosetron.mp. or Palonosetron/	765
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	9621
12	limit 11 to (english language and humans)	5631
13	limit 12 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	375
14	limit 13 to yr="2017 -Current"	95

Appendix 4: Key Inclusion Criteria

Population	Pediatric and adult patients with nausea and/or vomiting requiring an antiemetic, including indication such as post-op nausea and vomiting and chemotherapy induced nausea and vomiting.
Intervention	Newer antiemetics
Comparator	Active treatments or placebo
Outcomes	Absence of emesis or emesis reduction, incidence of nausea, need for rescue therapy and quality of life assessments
Timing	Prevention or treatment of nausea/vomiting
Setting	Inpatient and outpatient

Appendix 5: Prior Authorization Criteria

Antiemetics

Goal(s):

- Promote use of preferred antiemetics.
- Restrict use of costly antiemetic agents for appropriate indications.

Length of Authorization:

- Up to 6 months

Requires PA:

- Non-preferred drugs will be subject to PA criteria.

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org

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

2. Will the prescriber consider a change to the preferred product? Message: • Preferred products do not require a PA. • Preferred products are evidence-based and reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #3
3. Is the request for doxylamine/pyridoxine (Diclegis® or Bonjesta) for pregnancy-related nausea or vomiting?	**Yes:** Go to #4	**No:** Go to #5
4. Has the patient failed a trial of pyridoxine? Message: • Preferred vitamin B products do not require a PA. • Preferred products are evidence-based and reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Approve for up to 3 months	**No:** Pass to RPh; deny and recommend a trial of pyridoxine.
5. Is the request for dronabinol (Marinol®)?	**Yes:** Go to #6	**No:** Go to #7
6. Does the patient have anorexia associated with HIV/AIDS?	**Yes:** Approve for up to 6 months.*	**No:** Go to #7
7. Does the patient have a cancer diagnosis AND is receiving chemotherapy or radiation?	**Yes:** Approve for up to 6 months.	**No:** Go to #8
8. Does patient have refractory nausea/vomiting that has resulted in hospitalizations or ED visits?	**Yes:** Approve for up to 6 months.*	**No:** Go to #9
9. Has the patient tried and failed, or have contraindications, to at least 2 preferred antiemetics?	**Yes:** Approve for up to 6 months.*	**No:** Pass to RPh. Deny; medical appropriateness.

		Must trial at least 2 preferred antiemetics
* If the request is for dronabinol (Marinol®) do not exceed 3 doses/day for 2.5 mg and 5 mg strengths and 2 doses/day for the 10 mg strength.		

P&T/DUR Review: *2/21 (KS), 9/17 (KS); 1/17; 1/16; 11/14; 9/09; 2/06; 2/04; 11/03; 9/03; 5/03; 2/03*
Implementation: *TBD; 1/1/18; 4/1/17; 2/12/16; 1/1/15; 1/1/14; 1/1/10; 7/1/06; 3/20/06; 6/30/04; 3/1/04; 6/19/03; 4/1/03*

ProDUR Report for July through September 2020
High Level Summary by DUR Alert

DUR Alert	Example	Disposition	# Alerts	# Overrides	# Cancellations	# Non-Response	% of all DUR Alerts	% Overridden
DA (Drug/Allergy Interaction)	Amoxicillin billed and Penicillin allergy on patient profile	Set alert/Pay claim	10	5	0	5	0.01%	50.0%
DC (Drug/Inferred Disease Interaction)	Quetiapine billed and condition on file for Congenital Long QT Sundrome	Set alert/Pay claim	1,418	327	0	1,091	1.30%	23.1%
DD (Drug/Drug Interaction)	Linezolid being billed and patient is on an SNRI	Set alert/Pay claim	171	45	0	126	0.12%	26.3%
ER (Early Refill)	Previously filled 30 day supply and trying to refill after 20 days (80% = 24 days)	Set alert/Deny claim	72,900	14,125	21	58,749	68.03%	19.4%
ID (Ingredient Duplication)	Oxycodone IR 15mg billed and patient had Oxycodone 40mg ER filled in past month	Set alert/Pay claim	23,362	6,307	7	17,041	21.77%	27.0%
LD (Low Dose)	Divalproex 500mg ER billed for 250mg daily (#15 tabs for 30 day supply)	Set alert/Pay claim	681	126	0	555	0.57%	18.5%
LR (Late Refill/Underutilization)	Previously filled for 30 days supply and refill being billed 40 days later.	Set alert/Pay claim	5	3	0	2	0.01%	60.0%
MC (Drug/Disease Interaction)	Bupropion being billed and patient has a seizure disorder	Set alert/Pay claim	789	230	0	559	0.68%	29.2%
MX (Maximum Duration of Therapy)		Set alert/Pay claim	388	116	0	272	0.30%	29.9%
PG (Pregnancy/Drug Interaction)	Accutane billed and client has recent diagnosis history of pregnancy	Set alert/Deny claim	23	14	0	9	0.02%	60.9%
TD (Therapeutic Duplication)	Diazepam being billed and patient recently filled an Alprazolam claim.	Set alert/Pay claim	7,376	2,102	0	5,270	6.90%	28.5%
		Totals	**107,123**	**23,400**	**28**	**83,679**	**99.71%**	**21.8%**

ProDUR Report for July through September 2020

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)	1,370	234	1,136	11,890	11.5%	17.1%
ER	Lorazepam	391	105	286	12,185	3.2%	26.9%
ER	Alprazolam	190	41	149	7,714	2.5%	21.6%
ER	Diazepam	142	38	104	4,235	3.4%	26.8%
ER	Buspirone (Buspar)	2,664	475	2,189	26,807	9.9%	17.8%
ER	Lamictal (Lamotrigine)	4,549	833	3,716	37,344	12.2%	18.3%
ER	Seroquel (Quetiapine)	3,571	777	2,794	26,585	13.4%	21.8%
ER	Zyprexa (Olanzapine)	2,158	479	1,679	16,734	12.9%	22.2%
ER	Risperdal (Risperidone)	1,613	348	1,265	12,636	12.8%	21.6%
ER	Abilify (Aripiprazole)	2,852	512	2,340	23,324	12.2%	18.0%
ER	Wellbutrin (Bupropion)	4,690	795	3,895	54,429	8.6%	17.0%
ER	Hydrocodone/APAP	19	5	14	1,384	1.4%	26.3%
ER	Oxycodone	19	7	12	1,472	1.3%	36.8%
ER	Suboxone (Buprenorphine/Naloxone)	122	49	73	2,162	5.6%	40.2%
ER	Zoloft (Sertraline)	5,664	1,077	4,584	63,147	9.0%	19.0%
ER	Prozac (Fluoxetine)	3,824	587	3,237	43,823	8.7%	15.4%
ER	Lexapro (Escitalopram)	3,690	658	3,032	38,984	9.5%	17.8%
ER	Celexa (Citalopram)	1,933	291	1,642	24,232	8.0%	15.1%
ER	Trazodone	5,525	1,037	4,488	51,750	10.7%	18.8%
ER	Cymbalta (Duloxetine)	3,604	642	2,961	38,301	9.4%	17.8%
ER	Intuniv (Guanfacine)	1,499	207	1,292	11,098	13.5%	13.8%

ProDUR Report for July through September 2020

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	July	4,704	128	346	1,016	9	2,687	264	0	254
ER	August	2,810	81	188	551	4	1,669	210	0	107
ER	September	3,303	73	200	760	4	1,940	218	0	108
	Total =	**10,817**	**282**	**734**	**2,327**	**17**	**6,296**	**692**	**0**	**469**
	Percentage of total overrides =		**2.6%**	**6.8%**	**21.5%**	**0.2%**	**58.2%**	**6.4%**	**0.0%**	**4.3%**

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Retro-DUR Intervention History by Quarter FFY 2019 - 2020

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Change Form	Fluoxetine Tabs to Caps	Unique Prescribers Identified	953	367		172
		Unique Patients Identified	1202	384		192
		Total Faxes Successfully Sent	697	280		118
		Prescriptions Changed to Recommended Within 6 Months of Intervention	415	144		57
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$50,181	$12,113		$2,810
	Venlafaxine Tabs to Caps	Unique Prescribers Identified	341	96		345
		Unique Patients Identified	371	97		360
		Total Faxes Successfully Sent	256	76		235
		Prescriptions Changed to Recommended Within 6 Months of Intervention	159	59		141
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Intervention	$191,942	$66,872		$67,897

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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	Dose Optimization	Total Claims Identified	64	51	79	106
		Total Faxes Successfully Sent	40	25	45	33
		Prescriptions Changed to Recommended Dose Within 3 Months of Fax Sent	14	7	18	6
		Prescriptions Changed to Alternative Dose Within 3 Months of Fax Sent	12	5	9	11
		Prescriptions Unchanged after 3 Months of Fax Sent	34	27	41	33
		Safety Monitoring Profiles Identified	4	6	6	9
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Faxes Sent	$88,344	$81,541	$79,198	$8,112

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Retro-DUR Intervention History by Quarter FFY 2019 - 2020

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Expert Consultation Referral	Antipsychotic Use in Children	Total patients identified	990	675	1046	1470
		Profiles sent for expert review	10	5	11	9
		Prescribers successfully notified	8	5	7	9
		Patients with change in antipsychotic drug in following 90 days			2	
		Patients with continued antipsychotic therapy in the following 90 days	9	5	9	7
		Patients with discontinuation of antipsychotic therapy in the following 90 days	3		2	2

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Retro-DUR Intervention History by Quarter FFY 2019 - 2020

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Non-Adherence	Antipsychotics in people w/schizophrenia	Total patients identified	67	56	65	62
		Total prescribers identified	66	56	63	62
		Prescribers successfully notified	57	56	61	47
		Patients with claims for the same antipsychotic within the next 90 days	33	22	36	21
		Patients with claims for a different antipsychotic within the next 90 days	5	3	2	6

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Retro-DUR Intervention History by Quarter FFY 2019 - 2020

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Profile Review	Children under age 12 antipsychotic	RetroDUR_Profiles Reviewed	71	71	139	87
	Children under age 18 on 3 or more psychotropics	RetroDUR_Profiles Reviewed	17	6	19	8
	Children under age 18 on any psychotropic	RetroDUR_Profiles Reviewed	134	110	199	108
	Children under age 6 on any psychotropic	RetroDUR_Profiles Reviewed	9	8	13	12
	High Risk Patients - Opioids	RetroDUR_Profiles Reviewed		17	18	9
		RetroDUR_Letters Sent To Providers		5	7	6
		Provider Responses		0	0	0
		Provider Agreed / Found Info Useful		0	0	0
	High Risk Patients - Polypharmacy	RetroDUR_Profiles Reviewed	10	5		
		RetroDUR_Letters Sent To Providers	1			
		Provider Responses	0			
		Provider Agreed / Found Info Useful	0			
	Lock-In	RetroDUR_Profiles Reviewed	11	24	17	19
		RetroDUR_Letters Sent To Providers		2		
		Provider Responses		0		
		Provider Agreed / Found Info Useful		0		
		Locked In	0	2	0	0
	Polypharmacy	RetroDUR_Profiles Reviewed	29	36	2	21
		RetroDUR_Letters Sent To Providers	8	3		7
		Provider Responses	0	1		0
		Provider Agreed / Found Info Useful	0	1		0

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Retro-DUR Intervention History by Quarter FFY 2019 - 2020

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Safety Net	Combination Opioid-Sedative	Total patients identified	93	98	136	134
		Total prescribers identified	93	97	135	134
		Prescribers successfully notified	78	97	132	122
		Patients with discontinuation of therapy within next 90 days	15	13	22	36
		Patients with new prescription for naloxone within next 90 days	2	2	4	4
		Average number of sedative drugs dispensed within next 90 days	0	0	0	0
		Average number of sedative prescribers writing prescriptions in next 90 days	0	0	0	0
	ICS/LABA	Disqualified	2	4	5	4
		Disqualified - Erroneous denial	2	4	5	4
		Faxes Sent	2	1		1
		Fax Sent - Combination Inhaler	2	1		1
	TCAs in Children	Total patients identified		5	11	9
		Total prescribers identified		5	11	9
		Prescribers successfully notified		3	8	3
		Patients with claims for a TCA within the next 90 days		1	5	1
		Patients with claims for an alternate drug (SSRI, migraine prevention, or diabetic neuropathy) within the next 90 days			1	

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Optimizing the Use of NPH Insulin in Patients with Type 2 Diabetes Mellitus

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The Centers for Disease Control 2020 National Diabetes Report estimates individuals with diabetes represent 10.5% of the United States (US) population.[1] Improving glycemic control in these patients has a substantial impact on reducing co-morbidities and improving resource utilization. Appropriate product selection, with consideration of patient's payment mechanism, can be a crucial step in meeting therapy goals. The increasing burden of insulin costs is challenging for patients with limited resources. Insulin prices continue to rise, with a 262% increase in list prices and 51% jump in net prices (includes concessions/rebates made by the manufacturer when reporting sales) over the last two decades.[2] The incidence of cost-related medication non-adherence has been reported to be as high as 16.5% in adults with diabetes and 1.24 times more common in patients taking insulin compared to those not taking insulin.[3] NPH insulin, which is less costly than long-acting insulin analogs, is a valuable, underutilized therapeutic option. However, the long-acting insulin analogs, which are frequently perceived as superior products, are more commonly prescribed. This newsletter will discuss characteristics of NPH insulin products and strategies for providers to utilize when switching patients to NPH if appropriate.

NPH vs. Long-Acting Insulin Analogs

Either NPH insulin or a basal insulin analogs are an appropriate option for patients with type 2 diabetes mellitus (T2DM) requiring additional glucose lowering beyond oral therapies. Hemoglobin A1c (HbA1c) reductions between NPH insulin and basal insulin analogs are similar.[4] Clinical trial data suggests a modest benefit in reduced risk of nocturnal hypoglycemia with long-acting insulin analogs (glargine, detemir and degludec) compared to NPH insulin.[4] However, the incidence of severe hypoglycemia with long-acting insulin analogs and NPH in patients with T2DM is similar.[5] This was substantiated by a recent observational, retrospective review which analyzed the comparative hypoglycemia rates of long-acting insulin analogs (glargine or detemir) to NPH insulin.[5] Long-acting insulin analogs were associated with a 1.5% incidence of hypoglycemia-related emergency department visits or hospitalizations compared to 2.0% incidence with NPH insulin, the difference was not determined to be statistically or clinically different.[5] There is a lack of evidence to support clinically relevant differences for most outcomes when comparing long-acting insulin analogs to NPH. Additional comparative evidence between NPH and concentrated insulins (insulin glargine U-300) and ultra-long acting insulin (insulin degludec) is needed.[4]

NPH Insulin

If NPH is the most appropriate insulin option for a patient, there should be careful consideration related to initiating or switching therapy. The recommendation for initiating NPH insulin is 0.1 – 0.2 units per kilogram, which is most commonly started as a once daily dose at bedtime or twice daily .[6] Blood glucose monitoring should always accompany any insulin initiation or change. For most basal insulins, one fasting measurement daily is usually sufficient. NPH can be mixed with short or rapid acting insulin, reducing injections for patients.

Switching Between Insulin Products

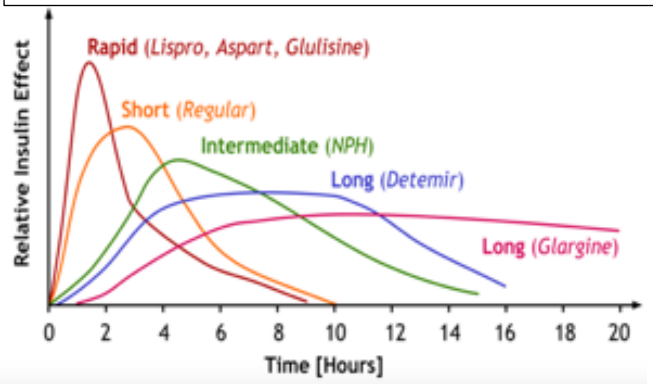
Consideration of insulin properties is an important step in the process of switching insulin. The duration of insulin action is important when changing a patient's regimen. **Table 1** and **Figure 1** provide insulin characteristics and dosing recommendations.

Table 1. Characteristics of Basal Insulin[6]

Basal Insulin	Duration of Action	Dosing Interval
NPH Insulins		
NOVOLIN N	Up to 24 hours	Once or twice daily
HUMULIN N	Up to 24 hours	Once or twice daily
Basal Insulin Analogs		
Insulin glargine (BASAGLAR, LANTUS)	Median 24 hours	Once daily
Insulin glargine U300 (TOUJEO)*	> 24 hours	Once daily
Insulin detemir (LEVEMIR)	7.6 – 24 hours (dose-dependent)	Once or twice daily
Insulin degludec (TRESIBA)	At least 42 hours	Once daily at any time

* Concentrated glargine formulation for patients requiring at least 20 units per day. May take up to 5 days to see maximal effect.

Figure 1. Duration of Action of Insulin Products[7]



There are many reasons for switching between insulin products, such as adverse reactions (e.g., hypoglycemia), cost, and insulin volume to be injected. If patients are switching between human insulin brands, such as Humulin N to Novolin N, the amount injected daily can be kept the same. If the patient has a history of hypoglycemia or no specific recommendations are available to facilitate switching insulins, reduction in insulin dose by 20% is a conservative approach to minimize adverse reactions. Specific recommendations for switching from basal insulins to NPH are provided in **Table 2.** Switching from NPH insulin to a different basal insulin is recommended for some patients because of clinical need, ease of use or cost-related factors (such as formulary or insurance preference). For this reason, guidance for switching from insulin NPH to a basal insulin analog is also presented in **Table 2**.

Table 2. Switching to or from NPH Insulin[8]

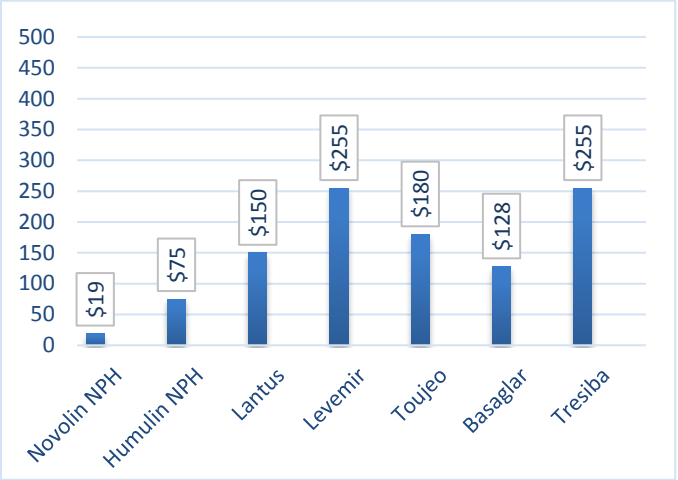
Product Switch	Conversion
Insulin detemir (LEVEMIR) to NPH	• Convert unit-per-unit* • Give NPH twice daily • Divide NPH dose equally or 2/3 in the AM and 1/3 before dinner or at bedtime • No specifics available for TOUJEO conversion. Consider 20% dose reduction
Insulin glargine U100 (LANTUS, BASAGLAR) or insulin glargine U300 (TOUJEO) to NPH	
Insulin degludec (TRESIBA) to NPH	• Limited information to guide switch • Consider unit-per-unit conversion • Give NPH twice daily • Divide NPH dose equally or 2/3 in the AM and 1/3 before dinner or at bedtime
NPH insulin to insulin glargine U100 (LANTUS, BASAGLAR) or insulin glargine U300 (TOUJEO)	• NPH given once daily can be switched unit-per-unit • NPH given twice daily should have total daily dose reduced by 20% and initiate new insulin as a once daily injection
NPH insulin to insulin detemir (LEVEMIR)	• Convert unit-per-unit • May need additional insulin detemir • Insulin detemir can be give once daily or divided twice daily
NPH insulin to insulin degludec (TRESIBA)	• Convert unit-per-unit and give once daily*

* Dose reduction of 20% in total daily dose is also recommended

Comparative Basal Insulin Costs

NPH insulin can be a low-cost option for uninsured patients and those that cycle on and off Oregon Health Plan (OHP) coverage. NPH may also represent an affordable insulin for patients with high deductible insurance plans, those on Medicare and when NPH is on a lower tier copay than branded products. ***Insurance plans may receive discounts on insulins; therefore, selection of the most cost-effective option should be individualized dependent on patient's insurance coverage.*** Costs of insulin products based on retail prices are displayed below in Figure 2.

Figure 2. RETAIL Basal Insulin Costs



* Prices based on cost for 25 units/day for 30 days (price for vials unless only available in pen formulation) from GoodRx.com. Accessed May 21, 2020.

- For OHP Fee-For-Service ***Lantus*** *is currently the most cost-effective basal insulin option followed by Levemir*
- For cash paying patients ***NPH insulin*** provides the most value

Conclusion

Insulin selection should be determined by patient specific characteristics. In the absence of a compelling need for a specific long-acting insulin product, value should be taken into account to reduce the economic burden for patients at risk for non-adherence due to resource constraints. There is no one basal insulin product that can be universally recommended for all patients. It is important to be mindful of the basal insulin that is the most clinically appropriate and represents the most cost-effective option.

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Shifts in the Treatment of Community Acquired Pneumonia

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Community-acquired pneumonia (CAP) is defined as a newly recognized pulmonary infiltrate with two or more symptoms that is acquired outside of the hospital setting. Empiric antibiotic treatment has traditionally centered around coverage for *Streptococcus pneumoniae (S. pneumoniae).* However, the proportion of cases attributable to *S. pneumoniae* has steadily declined over time since the use of the pneumococcal vaccine (5-15% of cases of CAP). Furthermore, a significant proportion of cases (20-25%) may be caused by respiratory viruses and there is ongoing debate about the need to cover for atypical pathogens.[1]

In late 2019, the Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS) updated the guideline for the diagnosis and treatment of adults with community-acquired pneumonia (CAP) for the first time since 2007.[2] The new guideline focuses on 16 specific areas for recommendations in diagnostic testing, appropriate site of care, initial empiric antibiotic therapy and consequent treatment decisions. The purpose of this newsletter is to discuss key changes in the management of CAP based on recent guidelines.

Removal of Health care-associated pneumonia (HCAP)

Health care-associated pneumonia (HCAP) was included in previous guidelines to identify patients at risk of pneumonia from multidrug-resistant pathogens due to exposure to various healthcare settings (nursing homes, dialysis centers, wound care, etc.). It was recommended to broaden empiric treatment for patients with HCAP and treat similar to hospital acquired pneumonia. Since then, studies have shown the risk factors used to define HCAP do not accurately predict the presence of multidrug resistant pathogens.[2] Additionally, this resulted in increased use of broad-spectrum antibiotics with no improvement in patient outcomes.[2]

The updated guideline removed the HCAP designation and instead recommends broadening coverage for methicillin resistant *Staphylococcus aureus* (MRSA) or *Pseudomonas aeruginosa (*P. *aeruginosa)* in adults with CAP only if locally validated risk factors are present.[2] The strongest risk factors are prior isolation of these organisms and hospitalization (or long-term care facility) with exposure to parenteral antibiotics in the last 90 days. Other potential drug pathogens that exhibit multidrug resistance should also be considered (*e.g. Enterococcus facium, Klebsiella pneumoniae, Acinetobacter baumannii, Enteroacter*). Lastly, it should be emphasized to deescalate broad spectrum antibiotic therapy at 48 hours consistent with microbiological results.

Table 1: Empiric Outpatient CAP Therapy[2]

Healthy Outpatients without comorbidities	Outpatients with comorbidities
• Amoxicillin 1gm TID, or • Doxycycline 100 mg BID	• Amoxicillin/clavulanate OR a cephalosporin PLUS a macrolide or doxycycline, or • Respiratory fluoroquinolone*
*levofloxacin 750 mg daily, moxifloxacin 400 mg daily	

Role of macrolides

The 2007 CAP guidelines included a strong recommendation for macrolide monotherapy for outpatients without comorbidities. In contrast, the updated guidelines include macrolide monotherapy as a conditional recommendation based on the local resistance of your area (< 25%) of *S. pneumoniae* to macrolides.[2] However, resistance is around 30% in most of the United States (including Oregon) and macrolide monotherapy should be discouraged in this patient population.[3] Furthermore, high dose amoxicillin (1 gm three times daily) is recommended for adults without comorbidities (**Table 1**). The higher dose overcomes resistant *S. pneumoniae* and studies have demonstrated efficacy of this regimen despite the lack of coverage for atypical organisms. An alternative to amoxicillin is doxycycline (**Table 1**).

Patients with comorbidities (chronic heart, lung, liver or renal disease; diabetes; alcoholism; malignancy) are more likely to experience poor outcomes if the initial antibiotic regimen is inadequate and may have risk factors for antibiotic resistance due to increased exposure to the healthcare system and/or prior antibiotic exposure. Therefore, the recommended regimen in the outpatient setting is a ß-lactam (amoxicillin/clavulanate, cefpodoxime, or cefuroxime) in combination with either a macrolide or doxycycline (**Table 1**), with only low quality evidence supporting doxycycline.[2] An alternative strategy is monotherapy with a respiratory fluoroquinolone. These combination regimens should adequately cover macrolide- and doxycycline-resistant *S. pneumoniae* since ß-lactam resistance is less common. It also covers atypical pathogens of interest, many enteric gram-negative bacilli and methicillin-susceptible *Staphylococcus aureus (*MSSA), and the addition of clavulanate provides coverage against ß-lactamase producing Haemophilus influenzae . Due to safety concerns (e.g. tendinopathy, peripheral neuropathy, significant hypoglycemia, central nervous system effects, and aortic aneurysm rupture) with fluoroquinolones, they should be reserved for situations when ß-lactams are not an option. If a patient has received an antibiotic within the previous 90 days, an antibiotic from a different class should be considered.

Empiric Therapy for Severe CAP

Empiric treatment for adult inpatients with nonsevere CAP and without risk factors for MRSA or *P. aeruginosa* remain largely unchanged since the 2007 guidelines (**Table 2**). The combination of a ß-lactam (e.g. ampicillin/sulbactam, ceftriaxone, ceftaroline) with a macrolide OR monotherapy with an antipneumococcal fluoroquinolone is recommended.[2] Preference is not given to one regimen over the other since data from noninferiority trials have demonstrated similar efficacy with ß--lactam/macrolide therapy compared to fluoroquinolone monotherapy. However, providers should consider the Food and Drug Administration (FDA) safety warnings associated with fluoroquinolones.

For inpatient adults with severe CAP, the updated guidelines cited higher quality evidence for the combination of a ß--lactam and a macrolide (moderate quality evidence) compared to a ß--lactam plus a respiratory fluoroquinolone (low quality evidence).[2] This minor change is supported by a possible mortality benefit seen with regimens including a macrolide in observational data.

Coverage for MRSA and/or *P. aeruginosa* should be added in patients with prior respiratory isolation and in those with recent hospitalization and parenteral antibiotics. Nasal PCR has a 99% negative predictive value and can be used to deescalate MRSA coverage. Only one antipseudomonal ß-lactam is needed for those with risk factors for *P. aeruginosa*.

Table 2: Empiric Inpatient CAP Therapy[2]

Inpatients (non-severe) without risk factors for MRSA or *P. aeruginosa*	Inpatients (severe*) without risk factors for MRSA or *P. aeruginosa*
• ß-lactam (ampicillin/sulbactam or ceftriaxone) PLUS macrolide, or • Respiratory fluoroquinolone	• ß-lactam (ampicillin/sulbactam or ceftriaxone) PLUS macrolide, or • ß-lactam PLUS respiratory fluoroquinolone
*Severe CAP includes either one major criterion (septic shock or mechanical ventilation) or three or more minor criteria (respiratory rate > 30, Pa_{02}/Fi_{02} ratio <250, multilobar infiltrates, confusion, uremia, leukopenia, thrombocytopenia, hypothermia, hypotension requiring fluid resuscitation)	

Use of Corticosteroids

The use of corticosteroids in CAP was not discussed in the 2007 ATS/IDSA guidelines. There are no data showing a benefit of corticosteroids in patients with nonsevere CAP and the updated guideline recommends against using corticosteroids in adults with nonsevere CAP (strong recommendation, high quality evidence).[2] They also do not recommended routine steroid use in severe CAP. However, this is only a conditional recommendation with low quality evidence based on inconsistent findings in the literature. While two randomized controlled trials (RCTs) demonstrated a reduction in mortality, length of stay, and organ failure, other RCTs have not shown an effect on clinically important outcomes and these results have not been replicated.[2] Results from published meta-analyses are also conflicting. With unclear data in severe CAP, the guideline does endorse the Surviving Sepsis Campaign recommendations for the use of corticosteroids in patients with septic shock refractory to fluid resuscitation and vasopressor support.[2]

Table 3: Summary of Changes to Treatment Recommendations[2]

Recommendation	2007 ATS/IDSA Guideline	2019 ATS/IDSA Guideline
Macrolide monotherapy	Strong recommendation for outpatients	Conditional recommendation for outpatients based on local resistance rates
Empiric therapy for severe CAP	ß-lactam PLUS macrolide and ß-lactam PLUS fluoroquinolone given equal weighting	Stronger evidence in favor of ß-lactam/macrolide combination
Use of HCAP Category	Accepted as per 2005 hospital-acquired pneumonia guidelines	Remove HCAP and focus on local epidemiology and validated risk factors for MRSA and *P. aeruginosa*
Use of corticosteroids	Not covered	Not universally recommended, consider in patients with septic shock

Aspiration Pneumonia

Aspiration pneumonia occurs with large-volume aspiration of colonized oropharyngeal or upper gastrointestinal contents leading to an infection. It is estimated that aspiration pneumonia causes 5-15% of CAP cases.[4] Risk factors include dysphagia; head, neck and esophageal cancer; chronic obstructive pulmonary diseases, impaired consciousness and seizures. The predominant pathogens in aspiration pneumonia were historically anaerobes. More recent studies have shown anaerobes are uncommon in patients with aspiration pneumonia. Instead, bacteria usually associated with CAP (*S. pneumoniae, Staphylococcus aureus, Haemophilus influenzae, and* Enterobacteriaceae) have been shown to be the main isolates in patients with aspiration pneumonia.[4]

Additionally, typical CAP coverage is active against the majority of gram-positive anaerobes found in the oropharyngeal tract. Additional anaerobic coverage would only be necessary if gram-negative anaerobes from the gastrointesntinal tract were suspected. Taking these things into account, the updated guidelines do not recommend routinely adding anaerobic coverage for aspiration pneumonia unless lung abscess or empyema is suspected.[2]

Duration

The guidelines recommend antibiotics for a minimum of 5 days and until the patient achieves clinical stability (normal vital signs, ability to eat and normal mentation).[2] Several small randomized trials with shorter courses of 5 days are noninferior to 7-8 days for the treatment of CAP.[2] Longer treatment courses should be considered for pneumonia complicated by meningitis, endocarditis and other deep-seated infection or infection with other, less common pathogens. Additionally, patients who fail to achieve clinical stability within 5 days should be evaluated for resistant pathogens, additional complications of pneumonia, or alternative source of infection.

Additional Diagnostic Updates

Changes in diagnosis and testing recommendations were also made to the 2019 guidelines. Previously, sputum and blood cultures were primarily recommended for patients with severe disease. In addition to patients with severe disease, the updated guidelines recommend collecting sputum and blood cultures in patients being empirically treated for MRSA or *P. aeruginosa* and in those with risk factors for MRSA or *P. aeruginosa.*[2] The goal of these recommendations is to identify resistant pathogens, narrow therapy, adjust therapy when appropriate, and to continue evaluation of the everchanging epidemiology of CAP.

While not discussed in the 2007 guideline, the use of procalcitonin is not recommended to determine the need for antibiotic initiation in the current guidelines. The literature regarding its ability to accurately distinguish between viral and bacterial etiology is mixed. If used to assist in the diagnosis and treatment of bacterial infection, appropriate protocols and education are needed to establish antibiotic de-escalation interventions. The guidelines reinforce that empiric antibiotics are recommended if CAP is clinically suspected and radiographically confirmed, regardless of procalcitonin level.

Lastly, the ATS/IDSA guideline update does not recommend routine use of follow-up chest imaging in patients whose symptoms have resolved and *Legionella* and Pneumococcal urinary antigen testing is not recommended for the majority of adults with CAP.

Conclusion

A summary of recent changes to the ATS/IDSA guideline for CAP is included in **Table 3**. The preferred regimens continue to focus on ß-lactams with or without a macrolide depending on level of care and comorbidities. Due to a myriad of potential adverse effects, fluoroquinolones should be reserved for when a ß-lactam is not an option. Changes in microbiologic patterns include more respiratory viruses contributing to CAP, increasing *S. pneumoniae* resistance to macrolides, and the fewer anaerobic pathogens contributing to aspiration pneumonia. Although several antibiotics have been FDA approved for CAP more recently (delafloxacin[5], lefamulin[6] and omadacycline[7]), the place in therapy of these agents is limited at this time until more data is available.

Peer Reviewed By: Jim Leggett, MD, Infectious Diseases, Providence Medical Center and Kendall Tucker, PharmD, MS, BCPS, BCIDP, Clinical Fellow Infectious Diseases and Epidemiology/Outcomes, OSU College of Pharmacy

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Asthma/COPD Drug Class Prior Authorization Update

Date of Review: December 2020 **Date of Last Review:** October 2020

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

Purpose for Prior Authorization Update:
In September 2020 Trelegy Ellipta (fluticasone furoate/umeclidinium/vilanterol) was approved for the maintenance treatment of asthma in patients 18 years and older, which necessitates changes to the prior authorization (PA) criteria to allow a pathway for obtainment.[1]

Summary of Approval:
The approval of the three drug product (inhaled corticosteroid [ICS]/long-acting muscarinic antagonist [LAMA]/ long-acting beta-agonist [LABA]), Trelegy Ellipta, was based on a double-blind, parallel-group, randomized controlled trial of 2,436 patients with asthma who were not controlled on ICS/LABA maintenance therapy in a study lasting 24 to 52 weeks.[1] The primary endpoint was change in trough forced expiratory volume in 1 second (FEV_1) at week 24. Trelegy Ellipta at the dose of fluticasone furoate 100 mcg/umeclidinium 62.5 mcg/vilanterol 25 mcg was found to increase trough FEV_1 more than fluticasone furoate 100 mcg/vilanterol 25 mcg by a least squares mean change (LSMC) of 110 mL (95% CI, 66 mL to 153 mL; P<0.001).[1] An FEV_1 change of 100 mL or more is considered clinically meaningful.[2] Comparison of Trelegy Ellipta at the dose of fluticasone furoate 200 mcg/umeclidinium 62.5 mcg/vilanterol 25 mcg reported a larger change in trough FEV_1 compared to fluticasone furoate 200 mcg/vilanterol 25 mcg (LSMC 92 mL (95% CI, 49 mL to 135 mL; P<0.001).[1] Trial results served as evidence for a new approved dose of Trelegy Ellipta (fluticasone Furoate/umeclidinium/vilanterol 200 mcg/62.5 mcg/25 mcg).[1]

Recommendations:
- No changes to the preferred drug list (PDL) are recommended.
- Modify ICS/LABA/LAMA PA criteria with updated indication for Trelegy Ellipta.

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Appendix 1: Current Preferred Drug List

LABA/LAMA Combination, Inhalers

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

Beta-agonists, Inhaled Long-acting

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

Anticholinergics, Inhaled

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

Corticosteroids, Inhaled

Generic	Brand	Form	PDL
budesonide	PULMICORT FLEXHALER	AER POW BA	Y

fluticasone propionate	FLOVENT DISKUS	BLST W/DEV	Y
fluticasone propionate	FLOVENT HFA	AER W/ADAP	Y
mometasone furoate	ASMANEX	AER POW BA	Y
beclomethasone dipropionate	QVAR REDIHALER	HFA AEROBA	N
budesonide	BUDESONIDE	AMPUL-NEB	N
budesonide	PULMICORT	AMPUL-NEB	N
ciclesonide	ALVESCO	HFA AER AD	N
fluticasone furoate	ARNUITY ELLIPTA	BLST W/DEV	N
mometasone furoate	ASMANEX HFA	HFA AER AD	N
fluticasone propionate	ARMONAIR DIGIHALER	INHAL PWD	N

Corticosteroid/LABA Combination, Inhalers

Generic	Brand	Form	PDL
budesonide/formoterol fumarate	BUDESONIDE-FORMOTEROL FUMARATE	HFA AER AD	Y
budesonide/formoterol fumarate	SYMBICORT	HFA AER AD	Y
fluticasone propion/salmeterol	ADVAIR DISKUS	BLST W/DEV	Y
fluticasone propion/salmeterol	ADVAIR HFA	HFA AER AD	Y
fluticasone propion/salmeterol	FLUTICASONE-SALMETEROL	BLST W/DEV	Y
fluticasone propion/salmeterol	WIXELA INHUB	BLST W/DEV	Y
mometasone/formoterol	DULERA	HFA AER AD	Y
fluticasone propion/salmeterol	AIRDUO RESPICLICK	AER POW BA	Y
fluticasone propion/salmeterol	FLUTICASONE-SALMETEROL	AER POW BA	N
fluticasone/vilanterol	BREO ELLIPTA	BLST W/DEV	N
Fluticasone propion/salmeterol	AIRDUO DIGIHALER	AER PW BAS	N

Miscellaneous Pulmonary Agents

Generic	Brand	Route	Form	PDL
montelukast sodium	MONTELUKAST SODIUM	PO	TAB CHEW	Y
montelukast sodium	MONTELUKAST SODIUM	PO	TABLET	Y
montelukast sodium	SINGULAIR	PO	TAB CHEW	Y
montelukast sodium	SINGULAIR	PO	TABLET	Y
benralizumab	FASENRA	SQ	SYRINGE	N
benralizumab	FASENRA PEN	SQ	AUTO INJCT	N
mepolizumab	NUCALA	SQ	AUTO INJCT	N
mepolizumab	NUCALA	SQ	SYRINGE	N
mepolizumab	NUCALA	SQ	VIAL	N
montelukast sodium	MONTELUKAST SODIUM	PO	GRAN PACK	N
montelukast sodium	SINGULAIR	PO	GRAN PACK	N

omalizumab	XOLAIR	SQ	SYRINGE	N
omalizumab	XOLAIR	SQ	VIAL	N
reslizumab	CINQAIR	IV	VIAL	N
roflumilast	DALIRESP	PO	TABLET	N
zafirlukast	ACCOLATE	PO	TABLET	N
zafirlukast	ZAFIRLUKAST	PO	TABLET	N
zileuton	ZILEUTON ER	PO	TBMP 12HR	N
zileuton	ZYFLO	PO	TABLET	N

Appendix 2: Prior Authorization Criteria

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

Goals:

- To optimize the safe and effective use of LAMA/LABA/ICS therapy in patients with asthma and COPD.
- Step-therapy required prior to coverage:
  - Asthma and COPD: short-acting bronchodilator and previous trial of two drug combination therapy (ICS/LABA, LABA/LAMA or ICS/LAMA). Preferred LAMA and LABA products do NOT require prior authorization.

Length of Authorization:

- Up to 12 months

Requires PA:

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

Covered Alternatives:

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

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

Approval Criteria		
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of preferred LAMA and LABA products in each class	**No:** Go to #3
3. Does the patient have a diagnosis of asthma or reactive airway disease without COPD?	**Yes:** Go to #9	**No:** Go to #4
4. Does the patient have a diagnosis of COPD, mucopurulent chronic bronchitis and/or emphysema?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review. Chronic bronchitis is unfunded.
5. Does the patient have an active prescription for an on-demand short-acting bronchodilator (anticholinergic or beta-agonist)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is the request for a LAMA/LABA combination product?	**Yes:** Go to #7	**No:** Go to #8
7. Is there a documented trial of a LAMA or LABA, or alternatively a trial of a fixed dose combination short-acting anticholinergic with beta-agonist (SAMA/SABA) (i.e., ipratropium/albuterol), or ≥ 2 moderate exacerbations or ≥ 1 leading to a hospitalization?	**Yes:** Approve for up to 12 months. Stop coverage of all other LAMA and LABA inhalers or scheduled SAMA/SABA inhalers (PRN SABA or SAMA permitted).	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
8. Is the request for a 3 drug ICS/LABA/LAMA combination product and is there a documented trial of a LAMA and LABA, or ICS and LABA or ICS and LAMA?	**Yes:** Approve for up to 12 months. Stop coverage of all other LAMA, LABA and ICS inhalers.	**No:** Pass to RPh. Deny; medical appropriateness.
9. Does the patient have an active prescription for an on-demand short-acting acting beta-agonist (SABA) and/or for ICS-formoterol?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness.
10. Is the request for Trelegy Ellipta (ICS/LAMA/LABA) combination product and is there a documented trial of an ICS/LABA?	**Yes:** Approve for up to 12 months. Stop coverage of all other LAMA, LABA and ICS inhalers.	**No:** Pass to RPh. Deny; medical appropriateness.

P&T Review: *12/20 (KS), 10/20 (KS), 5/19 (KS); 1/18; 9/16; 11/15; 9/15; 11/14; 11/13; 5/12; 9/09; 2/06*
Implementation: *3/1/18; 10/13/16; 1/1/16; 1/15; 1/14; 9/12; 1/10*

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Prior Authorization Criteria Update: Inflammatory Skin Conditions

Purpose of Update:

The Oregon Health Evidence Review Commission (HERC) revised Guideline Note 21 to broaden coverage of severe inflammatory skin disease in October 2020.[1] Inflammatory skin conditions in this guideline include: psoriasis, atopic dermatitis, lichen planus, Darier disease, pityriasis ruba pilaris, and discoid lupus. These conditions are funded on line 426 if they are severe, defined as having functional impairment AND one or more of the following:

A) At least 10% of body surface area involved
B) Hand, foot or mucous membrane involvement

The definition of functional impairment, previously defined as "inability to use hands or feet for activities of daily living, or significant facial involvement preventing normal social interaction", was replaced by an assessment of severe disease using the Dermatology Life Quality Index (DLQI) (score $\geq$ 11), Children's Dermatology Life Quality Index (CDLQI) (score $\geq$ 13),or severe score on another validated tool. [1]

If inflammatory skin conditions do not meet the criteria stipulated in Guideline Note 21, they are not funded by HERC and included on lines 480, 530, 539, and 654.

Recommendation:

- Revise PA criteria for biologic therapies, dupilumab, atopic dermatitis, and topical antipsoriatics to include an assessment of severe disease using a validated scoring tool such as the DLQI or CDLQI per HERC guidance.

References:

1. Oregon Health Evidence Review Commission. Coverage Guidance and Reports. http://www.oregon.gov/oha/hpa/csi-herc/pages/index.aspx Accessed October 14, 2020.

Prioritized List Guideline Note[1]

Extracted from the October 1, 2020 Prioritized List

GUIDELINE NOTE 21, SEVERE INFLAMMATORY SKIN DISEASE

Lines 426,482,504,532,541,656

Inflammatory skin conditions included in this guideline are:

A) Psoriasis
B) Atopic dermatitis
C) Lichen planus
D) Darier disease
E) Pityriasis rubra pilaris
F) Discoid lupus

The conditions above are included on Line 426 if severe, defined as having functional impairment as indicated by Dermatology Life Quality Index (DLQI) ≥ 11 or Children's Dermatology Life Quality Index (CDLQI) ≥ 13 (or severe score on other validated tool) AND one or more of the following:

C) At least 10% of body surface area involved
D) Hand, foot or mucous membrane involvement.

Otherwise, these conditions above are included on Lines 482, 504, 532, 541 and 656.

For severe psoriasis, first line agents include topical agents, phototherapy and methotrexate. Second line agents include other systemic agents and oral retinoids and should be limited to those who fail, or have contraindications to, or do not have access to first line agents. Biologics are included on this line only for the indication of severe plaque psoriasis; after documented failure of first line agents and failure of (or contraindications to) a second line agent.

For severe atopic dermatitis/eczema, first-line agents include topical moderate- to high- potency corticosteroids and narrowband UVB. Second line agents include topical calcineurin inhibitors (e.g. pimecrolimus, tacrolimus), topical phosphodiesterase (PDE)-4 inhibitors (e.g. crisaborole), and oral immunomodulatory therapy (e.g. cyclosporine, methotrexate, azathioprine, mycophenolate mofetil, or oral corticosteroids). Use of the topical second line agents (e.g. calcineurin inhibitors and phosphodiesterase (PDE)-4 inhibitors) should be limited to those who fail or have contraindications to first line agents. Biologic agents are included on this line for atopic dermatitis only after failure of or contraindications to at least one agent from each of the following three classes: 1) moderate to high potency topical corticosteroids, 2) topical calcineurin inhibitors or topical phosphodiesterase (PDE)-4 inhibitors, and 3) oral immunomodulator therapy.

Atopic Dermatitis and Topical Antipsoriatics

Goal(s):

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

Length of Authorization:

- From 6 to 12 months

Requires PA:

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

Covered Alternatives:

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

Table 1. FDA-approved ages for atopic dermatitis drugs

Drug	Minimum Age
Crisaborole	3 months
Pimecrolimus	2 years
Tacrolimus 0.03%	2 years
Tacrolimus 0.1%	16 years

Approval Criteria		
1. What diagnosis is being treated?	Record ICD 10 code.	
2. Is the diagnosis for seborrheic dermatitis, keratoderma or other hypertrophic and atrophic conditions of skin?	**Yes:** Pass to RPh; deny, not funded by the OHP.	**No:** Go to #3
3. Is the request for treatment of severe inflammatory skin disease? Severe disease is defined as:[1] • Having functional impairment as indicated by Dermatology Life Quality Index (DLQI) ≥ 11 or Children's Dermatology Life Quality Index (CDLQI) ≥ 13 (or severe score on other validated tool) ~~e.g. inability to use hands or feet for activities of daily living, or significant facial involvement preventing normal social interactio~~ AND one or more of the following: 1. At least 10% body surface area involved 2. Hand, foot or mucous membrane involvement	**Yes:** Go to #4	**No:** Pass to RPh; deny, not funded by the OHP
4. Is the diagnosis psoriasis?	**Yes:** Go to #8	**No:** Go to #5
5. Is the diagnosis atopic dermatitis?	**Yes:** Go to #6	**No:** Go to #10

Approval Criteria		
6. Does the patient meet the age requirements per the FDA label (Table 1)?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Does the patient have a documented contraindication, intolerance or failed trials of at least 2 first line agents indicated for the treatment of severe AD (topical corticosteroids)?* *Note pimecrolimus and crisaborole are FDA approved to manage mild to moderate AD, while tacrolimus is FDA approved to manage moderate to severe AD.	**Yes:** Document drug and dates trialed, and intolerances or contraindications (if applicable): 1._____(dates) 2._____(dates) Approve for length of treatment; maximum 6 months.	**No:** Pass to RPh. Deny; medical appropriateness
8. Is the requested product preferred?	**Yes:** Approve for length of treatment; maximum 1 year.	**No:** Go to #9
9. Will the prescriber consider a change to a preferred product? **Message:** Preferred products are evidence-based reviewed for comparative effectiveness & safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform provider of preferred alternatives. Approve for length of treatment; maximum 1 year.	**No**: Approve for length of treatment; maximum 1 year.

Approval Criteria		
10. RPH only: All other indications need to be evaluated as to whether they are funded by the OHP.*	**If funded, or clinic provides supporting literature:** Approve for 1 year.	**If not funded:** Deny, not funded by the OHP.

P&T/DUR Review: *12/20 (DM); 10/20; 7/19 (DM); 5/19 (DM) 3/18 (DM); 9/17; 7/15; 1/15; 09/10; 9/09; 3/09; 5/07; 2/06*

Implementation: *TBD, 11/1/20; 8/19/19; 4/16/18; 10/15; 8/15; 9/13; 6/12; 9/10; 1/10; 7/09; 6/07; 9/06*

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

References:

1.Oregon Health Evidence Review Commission. Coverage Guidance and Reports. http://www.oregon.gov/oha/hpa/csi-herc/pages/index.aspx Accessed October 14, 2020.

Dupilumab

Goal(s):

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

Length of Authorization:

- 6 months

Requires PA:

- Dupilumab (Dupixent®) 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. Maximum Adult Doses for Inhaled Corticosteroids.

High Dose Corticosteroids:	Maximum Dose
Qvar (beclomethasone)	320 mcg BID
Pulmicort Flexhaler (budesonide)	720 mcg BID
Alvesco (ciclesonide)	320 mcg BID
Aerospan (flunisolide)	320 mcg BID
Arnuity Ellipta (fluticasone furoate)	200 mcg daily
Flovent HFA (fluticasone propionate)	880 mcg BID
Flovent Diskus (fluticasone propionate)	1000 mcg BID

Asmanex Twisthaler (mometasone)	440 mcg BID
Asmanex HFA (mometasone)	400 mcg BID
High Dose Corticosteroid / Long-acting Beta-agonists	**Maximum Dose**
Symbicort (budesonide/formoterol)	320/9 mcg BID
Advair Diskus (fluticasone/salmeterol)	500/50 mcg BID
Advair HFA (fluticasone/salmeterol)	460/42 mcg BID
Breo Ellipta (fluticasone/vilanterol)	200/25 mcg daily
Dulera (mometasone/formoterol)	400/10 mcg BID

Table 2. FDA-approved ages for dupilumab.

Condition	**Minimum Age**
Asthma	12 years
Atopic dermatitis	6 years
Chronic rhinosinusitis with nasal polyposis	18 years

Approval Criteria	
1. What diagnosis is being treated?	Record ICD 10 code.

Approval Criteria		
2. Is the diagnosis an OHP funded diagnosis?	**Yes:** Go to #3	**No:** Pass to RPh. Deny, not funded by the OHP.
3. Is this a request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4
4. Is the medication being prescribed by or in consultation with a dermatologist, otolaryngologist, or allergist who specializes in management of severe asthma?	**Yes:** Go to # 5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the patient within FDA-approved age limits for the requested indication (**Table 2**)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is the diagnosis Severe Atopic Dermatitis (AD)? Severe disease is defined as:[1] • Having functional impairment as indicated by Dermatology Life Quality Index (DLQI) ≥ 11 or Children's Dermatology Life Quality Index (CDLQI) ≥ 13 (or severe score on other validated tool) ~~(e.g. inability to use hands or feet for activities of daily living, or significant facial involvement preventing normal social interaction)~~ AND one or more of the following: 1. At least 10% body surface area involved 2. Hand, foot or mucous membrane involvement	**Yes:** Go to #7	**No:** Go to #8

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

Approval Criteria		
10. Has the patient required at least 1 hospitalization or ≥ 2 ED visits in the past 12 months while receiving a maximally-dosed inhaled corticosteroid (Table 1) AND 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, or tiotropium)?	**Yes:** Go to #11 Document number of hospitalizations or ED visits in past 12 months: _____. This is the baseline value to compare to in renewal criteria.	**No:** Pass to RPh. Deny; medical appropriateness.
11. Has the patient been adherent to current asthma therapy in the past 12 months?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness.
12. Does the patient have chronic rhinosinusitis with nasal polyposis?	**Yes:** Go to # 13	**No:** Pass to RPh. Deny; medical appropriateness.
13. Has the patient failed medical therapy with intranasal corticosteroids (2 or more courses administered for 12 to 26 weeks[1])?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is the request to renew dupilumab for atopic dermatitis?	**Yes:** Go to #2	**No:** Go to #3

Renewal Criteria		
2. Have the patient's symptoms improved with dupilumab therapy? • at least a 50% reduction in the Eczema Area and Severity Index score (EASI 50) from when treatment started OR • at least a 4-point reduction in the Dermatology Life Quality Index (DLQI) from when treatment started OR • at least a 2 point improvement on the Investigators Global Assessment (IGA) score? OR • Dermatology Life Quality Index (DLQI) ≤11 or Children's Dermatology Life Quality Index (CDLQI) ≤ 13?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is the request to renew dupilumab for moderate to severe asthma?	**Yes:** Go to # 4	**No:** Go to # 6
4. Is the patient currently taking an inhaled corticosteroid and 2 additional controller drugs (i.e., long-acting inhaled beta-agonist, montelukast, zafirlukast, or tiotropium)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Has the patient reduced their systemic corticosteroid dose by ≥50% compared to baseline?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh. Deny; medical appropriateness.
6. Have the patient's symptoms of chronic rhinosinusitis with polyposis improved?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness.

1. Chong LY, Head K, Hopkins C, Philpott C, Burton MJ, Schilder AG. Different types of intranasal steroids for chronic rhinosinusitis. *Cochrane Database Syst Rev.* 2016; 4:Cd011993.

P&T/DUR Review: *12/20 (DM); 10/20; 11/19 (DM); 9/19; 7/19*

Implementation: *TBD, 11/1/20; 1/1/2020; 8/19/19*

1. *Oregon Health Evidence Review Commission. Coverage Guidance and Reports. http://www.oregon.gov/oha/hpa/csi-herc/pages/index.aspx Accessed October 14, 2020.*

Biologics for Autoimmune Diseases

Goal(s):

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

Length of Authorization:

- Up to 12 months

Requires PA:

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

Covered Alternatives:

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

Table 1. Approved and Funded Indications for Biologic Immunosuppressants.

Drug Name	Ankylosing Spondylitis	Crohn's Disease	Juvenile Idiopathic Arthritis	Plaque Psoriasis	Psoriatic Arthritis	Rheumatoid Arthritis	Ulcerative Colitis	Other
Abatacept (ORENCIA)			≥2 yo		≥18 yo	≥18 yo		
Adalimumab (HUMIRA) and biosimilars	≥18 y	≥6 yo (Humira) ≥18 yo (biosimilars)	≥2 yo (Humira) ≥4 yo (biosimilars)	≥18 yo	≥18 yo	≥18 yo	≥18 yo	Uveitis (non-infectious) ≥2 yo (Humira) HS ≥ 12 yo
Anakinra (KINERET)						≥18 yo		NOMID
Apremilast (OTEZLA)				≥18 yo	≥18 yo			Oral Ulcers associated with BD ≥ 18 yo
Baricitinib						≥18 yo		

Drug Name	Ankylosing Spondylitis	Crohn's Disease	Juvenile Idiopathic Arthritis	Plaque Psoriasis	Psoriatic Arthritis	Rheumatoid Arthritis	Ulcerative Colitis	Other
(OLUMIANT)								
Brodalumab (SILIQ)				≥18 yo				
Canakinumab (ILARIS)			≥2 yo					FCAS ≥4 yo MWS ≥4 yo TRAPS ≥ 4 yo HIDS ≥ 4 yo MKD ≥ 4 yo FMF ≥ 4 yo Stills Disease
Certolizumab (CIMZIA)	≥18 yo	≥18 yo		≥18 yo	≥18 yo	≥18 yo		Nr-axSpA ≥ 18 yo
Etanercept (ENBREL) and biosimilars	≥18 yo		≥2 yo	≥4 yo (Enbrel) ≥18 yo (biosimilars)	≥18 yo	≥18 yo		
Golimumab (SIMPONI and SIMPONI ARIA)	≥18 yo		≥2 yo active polyarticular course		≥218 yo	≥18 yo	≥18 yo (Simponi)	
Guselkumab (TREMFYA)				≥18 yo	≥18 yo			
Infliximab (REMICADE) and biosimilars	≥18 yo	≥6 yo		≥18 yo	≥18 yo	≥18 yo	≥6 yo	
Ixekizumab (TALTZ)	≥ 18 yo			≥6 yo	≥18 yo			Nr-axSpA ≥ 18 yo
Risankizumab-rzaa (SKYRIZI)				≥18 yo				
Rituximab (RITUXAN) and biosimilars						≥18 yo		CLL ≥18 yo NHL ≥18 yo GPA ≥2yo MPA ≥ 2 yo Pemphigus Vulgaris ≥18 yo (Rituxan only)
Sarilumab (KEVZARA)						≥18 yo		
Secukinumab (COSENTYX)	≥18 yo			≥18 yo	≥18 yo			Nr-AxSpA ≥18 yo
Tildrakizumab-asmn (ILUMYA)				≥18 yo				
Tocilizumab (ACTEMRA)			≥2 yo			≥18 yo		CRS ≥2 yo GCA ≥18 yo

Drug Name	Ankylosing Spondylitis	Crohn's Disease	Juvenile Idiopathic Arthritis	Plaque Psoriasis	Psoriatic Arthritis	Rheumatoid Arthritis	Ulcerative Colitis	Other
Tofacitinib (XELJANZ)			≥2 yo active polyarticular course		≥18 yo	≥18 yo	≥18 yo	
Upadacitinib (RINVOQ)						≥18 yo		
Ustekinumab (STELARA)		≥ 18 yo		≥12 yo	≥18 yo		≥18 yo	
Vedolizumab (ENTYVIO)		≥18 yo					≥18 yo	

Abbreviations: BD = Bechet's Disease; CLL = Chronic Lymphocytic Leukemia; CRS = Cytokine Release Syndrome; FCAS = Familial Cold Autoinflammatory Syndrome; FMF = Familial Mediterranean Fever; GCA = Giant Cell Arteritis; GPA = Granulomatosis with Polyangiitis (Wegener's Granulomatosis); HIDS: Hyperimmunoglobulin D Syndrome; HS: Hidradenitis Suppurativa; MKD = Mevalonate Kinase Deficiency; MPA = microscopic polyangiitis; MWS = Muckle-Wells Syndrome; NHL = Non-Hodgkin's Lymphoma; NOMID = Neonatal Onset Multi-Systemic Inflammatory Disease; nr-axSpA = non-radiographic axial spondyloarthritis; TRAPS = Tumor Necrosis Factor Receptor Associated Periodic Syndrome; yo = years old.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD-10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #4
4. Is the request for a non-preferred product and will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics Committee.	**Yes:** Inform prescriber of preferred alternatives.	**No:** Go to #5

Approval Criteria		
5. Has the patient been annually screened for latent or active tuberculosis and if positive, started tuberculosis treatment?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness. May approve for up to 3 months to allow time for screening.
6. Is the diagnosis Juvenile Idiopathic Arthritis, non-Hodgkin Lymphoma, Chronic Lymphocytic Leukemia, Non-infectious Posterior Uveitis, or one of the following syndromes: • Familial Cold Autoinflammatory Syndrome • Muckel-Wells Syndrome • Neonatal Onset Multi-Systemic Inflammatory Disease • Tumor Necrosis Factor Receptor Associated Periodic Syndrome • Hyperimmunoglobulin D Syndrome • Mevalonate Kinase Deficiency • Familial Mediterranean Fever • Giant Cell Arteritis • Cytokine Release Syndrome • Non-radiographic axial spondyloarthritis • Oral ulcers associated with Behcet's Disease • Still's disease AND Is the request for a drug FDA-approved for one of these conditions as defined in Table 1?	**Yes:** Approve for length of treatment.	**No:** Go to #7

Approval Criteria		
7. Is the diagnosis ankylosing spondylitis and the request for a drug FDA-approved for this condition as defined in Table 1?	**Yes:** Go to #8	**No:** Go to #9
8. If the request is for a non-preferred agent, has the patient failed to respond or had inadequate response to a Humira® product or an Enbrel® product after a trial of at least 3 months?	**Yes:** Approve for up to 6 months. Document therapy with dates.	**No:** Pass to RPh. Deny; medical appropriateness.
9. Is the diagnosis plaque psoriasis and the request for a drug FDA-approved for this condition as defined in Table 1? Note: Only treatment for *severe* plaque psoriasis is funded by the OHP.	**Yes:** Go to #10	**No**: Go to #12
10. Is the plaque psoriasis severe in nature, which has resulted in functional impairment as indicated by Dermatology Life Quality Index (DLQI) ≥ 11 or Children's Dermatology Life Quality Index (CDLQI) ≥ 13 (or severe score on other validated tool) AND one or ~~(e.g., inability to use hands or feet for activities of daily living, or significant facial involvement preventing normal social interaction) and one or~~ more of the following: • At least 10% body surface area involvement; or • Hand, foot or mucous membrane involvement?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; not funded by the OHP.

Approval Criteria		
11. Has the patient failed to respond or had inadequate response to each of the following first-line treatments: • Topical high potency corticosteroid (e.g., betamethasone dipropionate 0.05%, clobetasol propionate 0.05%, fluocinonide 0.05%, halcinonide 0.1%, halobetasol propionate 0.05%; triamcinolone 0.5%); and • At least one other topical agent: calcipotriene, tazarotene, anthralin; and • Phototherapy; and • At least one other systemic therapy: acitretin, cyclosporine, or methotrexate; and • One biologic agent: either a Humira® product or an Enbrel® product for at least 3 months?	**Yes**: Approve for up to 6 months. Document each therapy with dates.	**No:** Pass to RPh. Deny; medical appropriateness.
12. Is the diagnosis rheumatoid arthritis or psoriatic arthritis and the request for a drug FDA-approved for these conditions as defined in Table 1?	**Yes:** Go to #13	**No:** Go to #16

Approval Criteria		
13. Has the patient failed to respond or had inadequate response to at least one of the following medications: • Methotrexate, leflunomide, sulfasalazine or hydroxychloroquine for ≥ 6 months; or • Have a documented intolerance or contraindication to disease-modifying antirheumatic drugs (DMARDs)? AND • Had treatment failure with at least one biologic agent: a Humira® product or an Enbrel® product for at least 3 months? • AND • Is the patient on concurrent DMARD therapy with plans to continue concomitant use?	**Yes:** Go to #14 Document each therapy with dates. If applicable, document intolerance or contraindication(s).	**No:** Pass to RPh. Deny; medical appropriateness. Biologic therapy is recommended in combination with DMARDs (e.g. methotrexate) for those who have had inadequate response with DMARDs.
14. Is the request for tofacitinib, baricitinib, or upadacitinib?	**Yes:** Go to #15	**No:** Approve for up to 6 months
15. Is the patient currently on other biologic therapy or on a potent immunosuppressant like azathioprine, tacrolimus or cyclosporine? Note: Tofacitinib, baricitinib, and upadacitinib may be used concurrently with methotrexate or other nonbiologic DMARD drugs. Tofacitinib, baricitinib, or upadacitinib are not recommended to be used in combination with other JAK inhibitors, biologic DMARDs, azathioprine, or cyclosporine.	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve baricitinib or upadacitinib for up to 6 months. Approve tofacitinib for up to 6 months at a maximum dose of 10 or 11 mg daily for Rheumatoid Arthritis OR 10 mg twice daily for 8 weeks then 5 or 10 mg twice daily for Ulcerative Colitis

Approval Criteria		
16. Is the request for adalimumab in an adult with moderate-to-severe Hidradenitis Suppurativa (HS)?	**Yes:** Go to # 17	**No:** Go to # 18
17. Has the patient failed to respond, had inadequate response, or do they have an intolerance or contraindication to a 90 day trial of conventional HS therapy (e.g. oral antibiotics)? Note: Treatment of moderate-to-severe HS with adalimumab is funded on the Prioritized List of Health Services per Guideline Note 198	**Yes:** Approve for up to 12 weeks of therapy	**No:** Pass to RPh. Deny; medical appropriateness**.**
18. Is the diagnosis Crohn's disease or ulcerative colitis and the request for a drug FDA-approved for these conditions as defined in Table 1?	**Yes:** Go to # 19	**No:** Go to # 20
19. Has the patient failed to respond or had inadequate response to at least one of the following conventional immunosuppressive therapies for ≥6 months: • Mercaptopurine, azathioprine, or budesonide; or • Have a documented intolerance or contraindication to conventional therapy? AND • Has the patient tried and failed a 3 month trial of a Humira® product?	**Yes:** Approve for up to 12 months. Document each therapy with dates. If applicable, document intolerance or contraindication(s).	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
20. Is the diagnosis for an FDA approved diagnosis and age as outlined in Table 1, and is the requested drug rituximab for *induction or maintenance* of remission?	**Yes:** Approve for length of treatment.	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is the request for treatment of psoriatic arthritis or rheumatoid arthritis?	**Yes:** Go to # 4	**No:** Go to # 2
2. Is the request for continuation of adalimumab to treat moderate-to-severe Hidradenitis Suppurativa in an adult?	**Yes:** Go to # 3	**No:** Go to # 5
3. Has the patient had clear evidence of response to adalimumab therapy as evidenced by: A) a reduction of 25% or more in the total abscess and inflammatory nodule count, AND B) no increase in abscesses and draining fistulas.	**Yes:** Approve for an additional 12 weeks of therapy	**No:** Pass to RPh. Deny; medical appropriateness.
4. Has the patient been adherent to both biologic and DMARD therapy (if DMARD therapy has been prescribed in conjunction with the biologic therapy)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Has the patient's condition improved as assessed by the prescribing provider and provider attests to patient's improvement.	**Yes:** Approve for 6 months. Document baseline assessment and provider attestation received.	**No:** Pass to RPh; Deny; medical appropriateness.

P&T/DUR Review: *10/20 (DM); 2/20; 5/19; 1/19; 1/18; 7/17; 11/16; 9/16; 3/16; 7/15; 9/14; 8/12*

Implementation: ~~*TBD;*~~ *7/1/2019; 3/1/19; 3/1/18; 9/1/17; 1/1/17; 9/27/14; 2/2*

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Drug Class Update with New Drug Evaluation: Sedatives

Date of Review: December 2020

Date of Last Review: March 2017
Dates of Literature Search: 1/1/2017 - 4/23/2020
Brand Name (Manufacturer): DAYVIGO (Eisai Inc.)
Dossier Received: yes

Generic Name: lemborexant

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

Purpose for Class Update:
To review updated evidence for the sedatives drug class, including a new drug evaluation for DAYVIGO (lemborexant), in order to inform policy and placement of drugs on the Preferred Drug List (PDL) in the Oregon Health Plan (OHP) fee-for-service (FFS) population.

Research Questions:
1. What is the comparative evidence of efficacy or harms between sedatives when used for treatment of sleep disorders or for outpatient procedural sedation?
2. Are sedatives more effective or associated with more harms than no treatment when used for treat sleep disorders or for outpatient procedural sedation?
3. Are there subgroups of patients based on specific demographics, co-morbidities or other factors (e.g., age, co-morbid behavioral or mental disorders, concomitant medications, etc.) in which one sedative is more effective or associated with fewer adverse events than another sedative?

Conclusions:
- Six high-quality systematic reviews, two high-quality clinical practice guidelines, and one new drug approval were identified since the last drug class update in March 2017.
- Overall, there is still insufficient evidence of comparative efficacy and safety between specific drugs within this drug class.
- A systematic review found no improvement in sleep outcomes with eszopiclone or zolpidem in children with attention-deficit hyperactivity disorder (ADHD), with no improvement in ADHD symptoms, based on low-quality evidence.[1] While these drugs had higher frequency of some adverse events such as dizziness and hallucinations, the evidence was insufficient to draw conclusions.[1] Several trials identified in the review also provide low-quality evidence that melatonin may improve sleep latency and sleep duration in children, but evidence is insufficient to draw conclusions on improvements in nighttime awakenings or functional outcomes, or on increased frequency of some adverse events (e.g., dizziness, daytime drowsiness, and bed-wetting).[1] Children with autism or other neurodevelopmental disorders had the largest improvement in sleep outcomes with melatonin nightly.

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- A systematic review found that with the possible exception of melatonin, there is insufficient evidence for the use of sedatives in children with ADHD for treatment of sleeping disorders such as insomnia.[2] It was also found in this population that zolpidem and eszopiclone do not show significant improvement in different sleep parameters when compared with placebo but are associated with adverse effects.[2]
- A systematic review that evaluated sedatives for sleep disorders at high altitudes concluded that non-benzodiazepine sedatives were safe and superior to placebo in improving sleep quality at high altitudes based on moderate-quality evidence.[3] Patients who received zaleplon or zolpidem reported improvement in subjective sleep quality.[3] As measured by polysomnography (PSG), both zaleplon and zolpidem improved the total sleep time, sleep efficiency, and stage 4 sleep duration, whereas they decreased waking after sleep-onset without impairing ventilation.[3] In contrast, temazepam was not superior to placebo in terms of quicker onset of sleep and better sleep quality based on low-quality evidence.[3]
- A systematic review was performed to evaluated the efficacy and safety of the non-benzodiazepine sedatives eszopiclone, zaleplon, and zolpidem for sleep disorders in patients with schizophrenia.[4] Investigators concluded that eszopiclone may be useful for the treatment of insomnia symptoms in patients with schizophrenia, but the overall evidence is low quality.[4] Eszopiclone did not improve schizophrenia symptoms in any of the 3 studies.[4] They also advised against the use of other non-benzodiazepine drugs in this population because they have not been studied.[4]
- Two recent systematic reviews evaluated the association of sedative use and fractures: the objectives of one review[5] were to investigate the association between benzodiazepine use and benzodiazepine receptor agonist (BZRA) use and hip fracture risk; the second review[6] assessed the association between exposure BZRA use and the risk for fractures, falls and injuries. These systematic reviews found an increase in the association between both benzodiazepine and BZRA with hip fracture, general fractures, falls and injuries based on moderate quality evidence.[5,6] The risk of fracture depended on the length of time people used the drugs, with new users of these drugs at greatest risk of hip fracture.[5,6] There appears to be little difference in the findings between benzodiazepine and BZRAs based on low quality evidence.[5,6]
- The efficacy and relative efficacy of conscious sedation agents for behavior management in pediatric dentistry was evaluated in a systematic review. Meta-analysis of the available data from the primary outcome (behavior) was only possible for studies that investigated oral midazolam versus placebo.[7] From this meta-analysis, the investigators found moderate-quality evidence that the use of oral midazolam is associated with more cooperative behavior compared to placebo.[7] The investigators found insufficient evidence to draw any conclusions from studies that evaluated two or more sedatives for children needing dental care.[7]
- Cognitive Behavioral Therapy (CBT) is highly recommended as first-line therapy for chronic insomnia by both the American Academy of Sleep Medicine[8] and the European Sleep Research Society[9] based on high-quality evidence. A sedative can be offered if CBT is not effective or not available.[8,9] Orexin receptor antagonists (suvorexant), benzodiazepines (triazolam and temazepam only), BZRAs (eszopiclone, zaleplon, zolpidem), doxepin, and ramelteon are all weakly recommended to treat sleep onset and/or sleep maintenance insomnia based on low-quality evidence.[8] However, long-term treatment of chronic insomnia with a sedative is not recommended because of lack of evidence and possible adverse effects based on low-quality evidence.[9] Trazodone, and diphenhydramine are not recommended due to adverse effects and lack of efficacy, and there is insufficient evidence for use of melatonin in adults.[8]
- The U.S. Food and Drug Administration (FDA) applied black boxed warning labeling to BZRAs for complex sleep behaviors, including sleepwalking, sleep-driving, and engaging in other activities while not fully awake, which can lead to serious injuries, including death.[10]
- Lemborexant, an orexin receptor antagonist similar to suvorexant, was approved by the FDA in December 2019 for the treatment of insomnia in adults.[11] One trial found the decrease from baseline in latency to persistent sleep (LPS) as measured by PSG was larger and statistically significant for both lemborexant 5 mg (-19.5 min) and 10 mg (-21.5 min) doses compared to zolpidem extended-release (ER) 6.25 mg (-7.5 min) and placebo (-7.9 min).[12] A second trial found the decrease from baseline in subjective sleep onset latency (sSOL) was larger and statistically significant for both lemborexant 5 mg (-21.8 min) and 10 mg (-28.2 min) doses compared to placebo (-11.4 min).[13] These similar primary endpoints both provide low-quality evidence of efficacy for improved sleep onset, but it is important to note that secondary endpoints also found benefit in sleep maintenance outcomes.[12,13] The most common

adverse effect found with lemborexant was somnolence (8-13%), but most adverse events were mild in severity and did not appear to differ based on specific demographic characteristics of the study participants.[12]

Recommendations:

- Add melatonin as a preferred agent to the PDL based on relative evidence for safety and efficacy versus other sedatives in children with neurodevelopmental disorders.
- Update clinical prior authorization criteria in **Appendix 6**.
- Review comparative drug costs in the executive session.

Summary of Prior Reviews and Current Policy

- There is insufficient comparative evidence that assesses differences in efficacy or effectiveness between sedative classes or between individual sedative agents.
- Similar improvement in total sleep time was found with short-term use of benzodiazepines, non-benzodiazepine sedatives, and sedating antidepressants compared to placebo based on moderate-quality evidence.
- Sleep onset latency was improved in adults taking eszopiclone, zolpidem, ramelteon, suvorexant, and doxepin compared to placebo, but the mean sleep latency remained greater than 30 minutes in most trials.
- In elderly patients, there is low quality evidence that eszopiclone improves total sleep time and wake time after sleep onset compared to placebo. Sleep onset latency is improved with zolpidem and ramelteon compared to placebo in this population based on low quality evidence. Evidence also supports efficacy of doxepin for the treatment of insomnia in patients over 65 years of age.
- There is insufficient evidence to assess efficacy or safety of long-term use of sedatives. Few randomized control trials for non-benzodiazepine sedatives examine outcomes beyond 3 months, and study durations of benzodiazepines beyond 14 days were rare. Evidence from observational studies indicates long-term sedative use may be associated with increased risk of fractures and dementia. In addition, the FDA has recently updated warnings for non-benzodiazepine sedatives that emphasize the risk of rare but serious adverse effects including daytime memory and psychomotor impairment, abnormal thinking and behavior changes, complex behaviors (such as sleep driving), depression, and suicidal thoughts and actions.
- There is also insufficient evidence to compare efficacy of tapering regimens to improve rates of sedative discontinuation. Interventions to improve patient education and increase psychosocial support have improved rates of benzodiazepines discontinuation when used in combination with tapering strategies.
- Uncomplicated insomnia is an unfunded condition under the OHP unless it exacerbates or worsens a concomitant condition funded under the OHP. Current policy also prevents concomitant use of benzodiazepines, opioids or sedatives. Quantity limits apply for this class, including dose limits for zolpidem which is the only preferred drug in this class.

Background:

Insomnia is defined as dissatisfaction with sleep quantity or quality and is associated with difficulty initiating or maintaining sleep and early-morning waking with inability to return to sleep.[14] Approximately 6-10% of adults suffer from chronic insomnia, with most cases occurring in females and older adults.[9,14] Older adults are more likely to report problems with waking after sleep onset (WASO) (the sum of wake times from sleep onset to the final awakening [i.e., difficulty maintaining sleep]) than they are to report problems with sleep onset latency (SOL) (time to fall asleep). Sleep problems also occur in children, affecting about

25% of individuals during childhood, with a rate that is significantly higher in children with neurodevelopmental disorders, with prevalence estimates as high a 86%.[1]

Chronic insomnia poses substantial economic burdens on society.[8] Direct costs are attributed to significantly higher utilization of emergency and office health care visits as well as greater cost for prescription drugs.[8] Indirect costs are found in the form of work absenteeism, loss of productivity, and insomnia-related accidents.[8]

Insomnia is a risk factor for cardiovascular disease and has been associated with arterial hypertension, myocardial infarction and chronic heart failure.[9] Besides insomnia itself, there is evidence suggesting that short sleep duration (sleeping less than 6 hours on average) is a risk factor for obesity, type 2 diabetes, hypertension and cardiovascular diseases.[9]

Insomnia is also associated with increased risk for the development of major depressive disorder (odds ratio 2.1) and there are relationships between documented insomnia and suicidal ideation, suicide attempts and completed suicides.[9] Mental disorders, especially depression, bipolar disorder or psychosis frequently accompany sleep-onset or sleep-maintenance difficulties.[9] The presence of mental disorders should be examined in individuals complaining about insomnia. **Table 1** summarizes major somatic and mental co-morbidities of insomnia. [9]

Table 1. Major Co-morbidities of Insomnia.[9]

Psychiatric	Medical	Neurological	Substance Use/Dependence
Bipolar disorders	Chronic kidney diseases	Cerebrovascular diseases	Alcohol
Depressive disorders	Chronic pain	Fatal familial insomnia	Amphetamine
GAD	COPD	Multiple sclerosis	Caffeine
Panic disorder	Diabetes mellitus	Neurodegenerative diseases	Cocaine
PTSD	HIV	RLS	Designer drugs
Schizophrenia	Malignancy	Traumatic brain injury	Marijuana
	Rheumatic disorders		Nicotine
	Sleep apnea		Opioids

Abbreviations: COPD = chronic obstructive pulmonary diseases; HIV = human immunodeficiency virus infection; GAD = generalized anxiety disorder; PTSD = posttraumatic stress disorder; RLS = restless leg syndrome.

The Pittsburgh Sleep Quality Index (PSQI) can be used to assess subjective sleep; however, it is not a specific tool for diagnosing insomnia and should not be used for that purpose.[9] The Insomnia Severity Index (ISI) has been developed to assess the severity of the disorder, and has also been shown to be a reliable and valid instrument to detect patients with insomnia.[9] If indicated, actigraphy or PSG can be considered.[9] A meta-analysis of PSG-based studies showed that patients with insomnia have a significantly reduced total sleep time (TST), significantly prolonged SOL, and an increased number of nocturnal awakenings and amount of time awake during the night.[9] Furthermore, slow-wave sleep and REM sleep percentages are reduced compared with good sleepers.[9]

The goal of treatment for insomnia is to provide meaningful improvements in distress or dysfunction caused by the disorder.[14] The ISI and the PSQI also measure the distress and dysfunction associated with insomnia.[15] Sleep measures are based on specific sleep variables that can be assessed subjectively by patient-

reported sleep diaries or objectively in a sleep laboratory with PSG or actigraphy.[15] These include SOL, WASO, TST and sleep efficiency (percentage of time spent in bed sleeping; it is calculated as (TST / time in bed) × 100). **Table 2** addresses clinically meaningful outcomes for chronic insomnia.

Table 2. Clinically Meaningful Outcomes for Chronic Insomnia (Adapted from the American Academy of Sleep Medicine).[8]

Outcome (units)	Minimum Clinically Important Difference Versus Placebo^		
	Polysomnography (PSG)	Actigraphy	Subjective
Sleep Onset Latency (min)	10	10	20
Total Sleep Time (min)	20	20	30
Wake After Sleep Onset (min)	20	20	30
Quality of Sleep (varies*)	Varies	Varies	Varies
Sleep Efficiency (%)	5	5	10
Number of Awakenings (n)	2	2	0.5

^Clinical significance was judged to be present when a specific agent led to a mean change in the outcome of this magnitude, compared to placebo.
*For standardized mean difference (SMD), an effect size of 0.5 is considered clinically significant.

Sleep onset latency, when measured by PSG, may be reported as time to onset of first epoch of N1 (Stage 1) sleep, or, in more recent studies, as latency to persistent sleep (LPS), or time to onset of first 10 consecutive minutes of sleep.[8] Total sleep time, as mentioned earlier, is defined as the total time spent in bed, minus SOL and WASO.[8] Quality of sleep is a patient-reported measure, the definition of which varies by measurement tools and patient perceptions.[8] Lastly, the number of awakenings is defined as the number of awakenings after sleep onset, excluding the final awakening.[8]

Assessment of the efficacy of a given agent for the treatment of chronic insomnia is challenging, and it remains unclear which are the most important variables for defining drug efficacy.[8] More specific efficacy endpoints for both patient-reported and objective outcomes have been utilized in studies recently (e.g., self-reported and PSG-based SOL, WASO and TST), but substantial variability in data reporting is not uncommon.[8] Several unresolved issues remain: first, investigators have not fully agreed upon the relative importance of subjective versus objective data; secondly, it is unknown whether sleep quality endpoints are better evaluated using subjective or objective means, and if sleep quality is more meaningful than measures of SOL, TST or WASO; thirdly, an additional issue is whether efficacy is better reflected by measures of daytime alertness and cognitive, emotional, and psychomotor function than by measures of sleep.[8] Lastly, insomnia disorder is generally treated on the basis of patient-reported sleep-associated distress in clinical practice, not laboratory assessment.[15]

The standard of treatment for insomnia is CBT, but pharmacotherapy is also frequently used to treat insomnia.[8] Although FDA-approved medication indications often focus on specific sleep variables, it is not known how frequently primary care physicians target medications to specific or global measures of insomnia or prescribe them long-term.[15] Many patients may also self-treat using medications or substances like alcohol which have not shown to be effective in management of insomnia or have significant potential for harm.[8] About 3.5% to 7% of individuals are prescribed drugs for sleep disturbances, but there continues to be significant knowledge gaps and anxieties about the proper use of these drugs among providers.[8] A summary of the PDL for this drug class is in **Appendix 1**. Sedatives used in clinical practice, but not included in this drug class, are the antidepressants trazodone and mirtazapine, the antipsychotics olanzapine and quetiapine, and the supplement melatonin.

In the second quarter of 2020 (4/1/2020 to 6/30/2020), there were 348 patients with a FFS request for an agent in the sedative PDL class. Fifty percent of patients (n=176) had requests for a non-preferred agent. The most common non-preferred agents included triazolam (n=27) and first-generation antihistamines

doxylamine or diphenhydramine (n=44). Approximately 36% of patients (n=125) had no delay in therapy, and up to 48% of patients (n=167) had a paid claim within 90 days, with the majority of paid claims for preferred zolpidem products. Of the patients with paid claims for a sedative, 4 requests were for adolescents 13 to 17 years of age, and 2 requests were for children (ages 2 and 5 respectively). Fifty-two percent of patients never received a paid claim for a sedative. In patients without a subsequent paid claim, 31% were transferred into a coordinated care organization, 5% lost eligibility, and 34% had other insurance which may have paid for their claims. For 28% of patients (n=51), a PA was never requested by their provider.

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:
Sedatives in Children with Insomnia
The Drug Review Effectiveness Project systematically reviewed the evidence of sedatives in children with insomnia.[1] Randomized, head-to-head or placebo-controlled trials of at least 1-week duration or systematic reviews that evaluated sedatives in children and adolescents (age <18 years) with sleep disorders were eligible for inclusion.[1] Drugs included: 1) melatonin agonists ramelteon and melatonin; 2) non-benzodiazepine sedatives eszopiclone, zaleplon and zolpidem; and 3) orexin receptor antagonist suvorexant. Efficacy outcomes of interest included: 1) sleep latency; 2) sleep duration; 3) number of awakenings; and 4) functional status (e.g. daytime alertness, missed school).[1] Safety outcomes of interest included: 1) study withdrawals due to adverse events; 2) serious adverse events, and 3) specific adverse events (e.g. sleep walking, rebound insomnia, cognitive impairment).[1] Studies conducted in sleep labs were excluded.[1]

Twenty-one placebo-controlled RCTs were identified that provide evidence for eszopiclone (n=1), zolpidem (n=1) and melatonin (n=19).[1] No head-to-head comparative evidence of sedatives in children with sleep disorders were found.[1] Six trials identified children with a diagnosis of chronic sleep-onset insomnia, although many of the participants had comorbid conditions like ADHD.[1] The remaining trials included children with both sleep problems and a specific co-morbid diagnosis: 3 studies enrolled children with ADHD, 4 studies included children with autism spectrum disorders with other neurodevelopmental disorders, 2 studies enrolled children with epilepsy, and one trial included children with atopic dermatitis.[1] Study durations ranged from 1 week to 12 weeks.[1] Two studies enrolled adolescents, while the mean age in the other studies was 9 years.[1] The two studies that evaluated eszopiclone and zolpidem included 201 and 468 participants, respectively.[1] The trials that evaluated melatonin were smaller, ranging from 8 to 160 children.[1] The daily dose of melatonin ranged widely, from 2 to 12 mg.[1]

The manufacturers for eszopiclone and zolpidem funded both studies, and both were conducted in the U.S.[1] The studies enrolled children 6 to 17 years of age who had insomnia and an ADHD diagnosis.[1] Children were taking psychostimulants for ADHD symptoms.[1] Sleep outcomes were measured by PSG and actigraphy, while outcomes for behavior were based on subjective child and parent assessments.[1] Neither eszopiclone nor zolpidem improved sleep or ADHD

outcomes, although Clinical Global Impression score for Improvement (CGI-I), which is a 7-point scale that assesses improvement from baseline, did favor both drugs.[1] More children who received zolpidem (7.4%) withdrew from the study early compared to placebo (0%).[1] Dizziness, headache, hallucinations, and anxiety were reported with zolpidem more frequently than with placebo, while somnolence, dizziness, and hallucinations were reported more frequently with eszopiclone.[1] The investigators graded the evidence for these findings as low for sleep outcomes and ADHD ratings, and insufficient for adverse events.[1]

Melatonin improved sleep outcomes more than placebo across several fair- and good-quality studies.[1] Sleep latency (time to fall asleep) improved by 11 to 51 minutes (median 33.75 minutes), and most of these studies found a statistically significant difference.[1] Sleep duration also improved, by a median of 23 minutes (range, 13 to 93 min), with 67% of studies finding the difference to be statistically significant.[1] Children with autism had the largest improvement in sleep outcomes (reduced sleep latency by 38 minutes, longer sleep duration by 5.5 minutes) with 3 mg to 10 mg of melatonin nightly.[1] Other specific populations found benefit with melatonin: sleep latency improved by 21 minutes in children with chronic sleep-onset insomnia, 24 minutes in children with other neurodevelopmental disorders including ADHD, 11 minutes in children with epilepsy, and 21 minutes in children with atopic dermatitis.[1] Sleep duration improved by 36.7 and 33.4 minutes with other neurodevelopmental disorders and ADHD, 23.2 and 24.8 minutes with epilepsy and atopic dermatitis, and 15.5 minutes with chronic sleep onset insomnia.[1] The number of nighttime awakenings was not improved across 8 studies that evaluated that outcome, but WASO was improved from 8.2 to 31.9 minutes based on evidence from 4 studies (3 studies found a statistically significant difference).[1] Melatonin did not consistently improve functional outcomes across 7 studies that evaluated these outcomes.[1] However, these outcomes were more favorable in children with autism or other neurodevelopmental disorders.[1] Adverse events with melatonin were infrequent, but those events that were more common with melatonin than placebo included dizziness, daytime drowsiness or reduced alertness, and bed-wetting complaints.[1] No differences in early study withdraw due to adverse events were found between children treated with melatonin and those treated with placebo.[1] The investigators graded the evidence for these findings as low for sleep latency and sleep duration, but insufficient for outcomes related to nighttime awakenings, functional outcomes, and adverse events.[1]

<u>Sedation of Children Undergoing Dental Treatment</u>

Sedation may be used to relieve anxiety and manage behavior in children undergoing dental treatment.[7] In 2005, the Cochrane Collaboration identified a need to determine from published research which sedatives, dosages and regimens are effective, which was subsequently first updated in 2012 and updated again in 2018.[7] The objective of this 2018 systematic review was to evaluate the efficacy and relative efficacy of conscious sedation agents and dosages for behavior management in pediatric dentistry.[7]

Studies were selected if they were a RCT of conscious sedation that compared two or more drugs, the same drug with different dosages, or a single drug controlled by placebo or another technique to manage behavior.[7] Drugs had to be administered by a dentist or anesthetist in an outpatient setting or dental office.[7] The following pediatric population was specifically reviewed:

- Children and adolescents aged 0 to 16 years of age (including children with specific medical or behavioral problems); and
- Simple dental restorative treatment with local anesthesia (e.g. fillings, stainless steel crowns), simple extractions or management of dental trauma (e.g. repositioning of tooth, splinting, removal of nerve from tooth).[7]

The primary outcome was behavior, which is measured by a range of different indices.[7] Secondary outcomes included dental treatment completion, postoperative anxiety, and adverse events.[7] Dichotomous outcomes such as treatment completion were compared by calculating risk ratios (RR) along with 95% confidence intervals (CI).[7] Continuous outcomes (e.g. Frankl behavior scale) were reported as mean and standard deviations (SD) in each group.[7] Because of the wide range of scales used to measure sedation in studies, the Houpt Scale was taken as the standard when ranking behavior (i.e. higher values equal better behavior).[7] Where scales ran in the reverse order, values were transformed so that higher values equaled better behavior (e.g. anxiety scores as measured on

the Venham scale were transformed by subtracting the mean score per group from the maximum possible score).[7] Where dosage studies were analyzed, the lowest dose was compared to the highest dose.[7] Results from the lowest dosage were listed first.[7] The certainty of the evidence was assessed using GRADE methodology.[7]

The 50 included studies were undertaken in 16 different countries with the greatest proportion of studies (n = 12, 24%) from the US.[7] Age of participants included in the trials ranged from 1 year to 16 years.[7] Mean age for all studies was 4.8 years.[7] The mean number of participants per study was 74.08 (standard deviation (SD) = 109) with a total of 3704 children randomized in the 50 included trials.[7] Forty studies (81%) were at high risk of bias, 9 studies (18%) were at unclear risk of bias, and just one study was assessed at low risk of bias.[7] There were 34 different sedatives used with or without inhalational nitrous oxide.[7] Dosages, mode of administration and time of administration varied widely.[7] Studies were grouped into placebo-controlled, dosage comparisons and head-to-head comparisons.[7] In most of the studies (n = 39, 78%), patients were reported as being uncooperative or anxious at the beginning of the study based on the Frankl behavioral rating scale often used to measure baseline behavior.[7]

Of the outcome measures proposed for this review (difference in behavior, completion of treatment, difference in postoperative anxiety, and adverse events), meaningful data could only be extracted on behavior.[7] Postoperative anxiety was rarely mentioned, and in most of the studies almost all the participants completed treatment.[7] Outcome variables reported in the studies were mostly ordinal (e.g. 5-point scale for increasing movement) or dichotomous (e.g. success/failure).[7] Measures of behavior or level of sedation scales were commonly used (Houpt or modified versions of Houpt were used most frequently).[7] Adverse events were recorded but this was not done in a uniform manner between studies.[7]

There were 12 placebo-controlled studies which investigated oral midazolam, oral chloral hydrate, oral diazepam, melatonin, intranasal dexmedetomidine, intramuscular meperidine, intravenous midazolam, midazolam/ketamine, and inhaled nitrous oxide.[7] Ten studies compared different dosages or routes of administration of sedative agents: one used hydroxyzine and the other studies used various dosages and methods of administration of midazolam.[7] A summary of the findings of oral agents utilized on the PDMP are in **Table 3** and **Table 4**.

Meta-analysis of the available data from the primary outcome (behavior) was only possible for studies that investigated oral midazolam versus placebo.[7] From this meta-analysis, the investigators found moderate-certainty evidence from 6 small, clinically heterogeneous studies at high or unclear risk of bias, that the use of oral midazolam in doses between 0.25 mg/kg to 1 mg/kg is associated with more cooperative behavior compared to placebo; the standardized mean difference (SMD) favored midazolam (SMD 1.96; 95% CI, 1.59 to 2.33, $p<0.0001$, $I^2 = 90\%$; 6 studies; 202 participants).[7] It was not possible to draw conclusions regarding the secondary outcomes due to inconsistent or inadequate reporting.[7]

Table 3. Sedative Compared to Placebo in Children Needing Dental Care (adapted from Cochrane).[7]

Drug and Outcome	Anticipated Absolute Effects* (95% CI)		Relative Effect (95% CI)	Number of Participants	Certainty of Evidence (GRADE)	Comments
	Risk with Placebo	Risk with Sedative				
Midazolam, oral Houpt/other behavioral score SD units: investigators measure behavior using different scales – higher values mean better behavior	1.96 SDs higher (1.59 to 2.33 SDs higher) than the placebo group		-	202 (6 RCTs)	MODERATE	As a rule of thumb, 0.2 SD represents a small difference, 0.5 a moderate difference, and 0.8 a large difference. Adverse events: vomiting/hiccupping reported in one study. Amnesia reported in one study. Oral midazolam probably improves behavior
Diazepam, oral Houpt/other behavioral score	0.62 SDs higher (0.28 lower to 1.53 higher) than the placebo group		-	20 (1 RCT)	VERY LOW	No adverse events reported. Uncertain whether oral diazepam improves behavior.
Chloral hydrate, oral Good or better behavior	533 per 1000	709 per 1000 (427 to 1000)	RR 1.33 (0.8 to 2.22)	60 (1 RCT)	VERY LOW	Adverse events: associated with airway problems. Uncertain whether chloral hydrate improves behavior.

***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
Abbreviations: CI = confidence interval; RCT = randomized controlled trial; RR = risk ratio; SD: standard deviation; SMD = standardized mean difference.

Table 4. Sedative Compared with Different Dosage of the Same Sedative for Children Needing Dental Care.[7]

Drug and Outcome	Number of Participants (studies)	Certainty of Evidence (GRADE)	Comments
Midazolam (any route of administration) Any behavioral score	394 (10)	VERY LOW	There is insufficient evidence to determine whether any specific dose of intranasal midazolam is more effective than another. There is weak evidence from two trials that oral midazolam at a dose of 0.5 mg/kg to 0.75 mg/kg is effective. One trial administered both nitrous oxide and midazolam, so it is difficult to attribute benefit to midazolam alone.
Any behavioral score – hydroxyzine	30 (1)	VERY LOW	There is insufficient evidence to determine whether any specific dose of hydroxyzine is effective.

No studies that compared two or more sedatives of the same intervention found similar effect.[7] Overall, there was insufficient evidence to draw any conclusions from studies that evaluated two or more sedatives for children needing dental care.[7]

Sedatives for Treatment of Behavioral Insomnia in Children with Attention-Deficit Hyperactivity Disorder

A systematic review that assessed the safety, tolerability and efficacy of the most commonly used drugs to treat behavioral insomnia associated with ADHD was performed.[2] The review focused on sleep-onset insomnia (SOI), total sleep duration and number of awakenings during the night.[2] Observational and interventional studies that investigated the effects of melatonin, zolpidem, and eszopiclone on behavioral insomnia in children with ADHD were included.[2] ADHD was defined according to criteria outlined by the Diagnostic and Statistical Manual (DSM) of Mental Disorders, the American Academy of Child and Adolescent Psychiatry, the Diagnostic Interview Schedule for Children Version IV, or parents' and teachers' report on the child symptom inventories.[2] In order to ensure methodological quality and to avoid the bias caused by dependence on investigators agreeing to provide data from unpublished studies, only published, peer-reviewed studies were included.[2] Twelve studies, either observational studies or RCTs, met the inclusion criteria for this systematic review.[2]

In one good-quality, placebo-controlled melatonin trial, mean SOL and TST improved by both objective and subjective measurements in children with ADHD who did not respond adequately to sleep hygiene measures.[2] The mean SOL improved by about 16 minutes and TST improved by about 15 minutes, with melatonin versus placebo.[2] Open-label follow-up did not show a significant improvement in SOL; however, the improvement in sleep duration by 23 minutes continued with the melatonin treatment.[2] Another good-quality RCT found a difference in TST of about 33 minutes between melatonin and placebo.[2] Compared with placebo, the melatonin group had a statistically significant decrease in SOL ($p = 0.001$), increase in sleep efficiency ($p = 0.01$) and decrease in nocturnal restlessness ($p = 0.03$).[2] Observational studies have also found improvement in SOL with melatonin in children with ADHD based on subjective measurements.[2] One study found that mean SOL decreased with melatonin versus placebo at week 8 (26 min vs. 18 min, respectively), and mean TST increased with melatonin by about 0.5 hours but decreased with placebo by about 0.5 hours.[2] In another study, almost 90% of parents were satisfied with melatonin for the improvement of sleep-onset problems, 70.8% were satisfied with melatonin for improved daytime behaviors, and 60.9% for improvement of mood.[2] These studies have found that melatonin improves chronic behavioral insomnia in children with ADHD only as long as treatment is continued, but did not cure it, as relapse was common once treatment stopped.[2] Adverse events with melatonin have usually been mild and similar to those with placebo; however, studies have not been powered adequately to allow any definitive evaluation of safety related to melatonin.[2]

No statistically significant differences in LPS or TST between the zolpidem and placebo was detected at week 4 by actigraphy (objective) measures in children with ADHD-associated insomnia based on a good-quality RCT.[2] At week 4, the baseline-adjusted least square mean difference ± standard error for TST (i.e. TST minus baseline TST) was 2.77 ± 14.23 min ($p = 0.8461$), and for LPS was 1.55 ± 110.37 min, ($p = 0.8884$).[2] Treatment-emergent adverse events (TEAE) were reported in 62.5% and 47.7% of children treated with zolpidem and placebo, respectively.[2] Treatment discontinuation occurred in 10 children in the zolpidem group versus none in the placebo group, the primary adverse event being hallucinations, which occurred in 10 of 136 total patients. Other adverse events included dizziness and headache.[2]

No statistically significant differences between eszopiclone and placebo at week 12 were found in PSG-measured LPS in an excellent quality RCT in children with ADHD-associated insomnia.[2] Secondary subjective measures (patient/parent reports on SOL, TST, WASO, number of awakenings after sleep onset and sleep quality) revealed no statistically significant differences on hierarchical statistical analysis.[2] The most common TEAE in this study were headache, dysgeusia and dizziness, which were reported more commonly in the eszopiclone groups (about 60% versus 46% with placebo).[2] Of interest, several patients discontinued treatment due to hallucinations (2.3%) and suicidal ideation (1%) in the eszopiclone-treated groups.[2]

The results from these RCTs and observational studies indicate that the quality of most of the available studies for the drugs treating behavioral insomnia in children with ADHD is not very high.[2] With the possible exception of melatonin, there is insufficient evidence for the use of sedatives in treating sleep-related

disturbances such as insomnia in ADHD.[2] It was also found that zolpidem and eszopiclone did not show significant improvement in different sleep parameters when compared with placebo but were associated with TEAEs.[2]

Benzodiazepine Receptor Agonist Sedatives for Improving Sleep Quality in Patients with Schizophrenia

About 44% of patients with schizophrenia suffer from sleep disturbances.[4] This systematic review and meta-analysis was performed to inform clinical practice on the efficacy and safety of the benzodiazepine receptor agonists (BZRA) eszopiclone, zaleplon, and zolpidem for schizophrenia.[4] Outcomes of importance were: 1) improvement in overall schizophrenia symptoms; 2) improvement in insomnia symptoms; 3) discontinuation rate; and 4) individual adverse events.[4] Only RCTs of Z-drugs for patients with schizophrenia were included in this study.[4] Non-blinded randomized trials were not excluded in order for the investigators to obtain as much information as possible.[4] If outcome data were reported by at least 2 RCTs, a meta-analysis was performed to combine pooled data of these drugs versus placebo).[4] The primary outcome measure was all-cause study discontinuation.[4] Secondary outcomes for efficacy were improvement in the overall schizophrenia symptoms [Brief Psychiatric Rating Scale (BPRS) and Positive and Negative Symptom Scale (PANSS) scores], total sleep time, and WASO.[4] Secondary outcomes for safety were discontinuation due to adverse events and individual adverse events (incidence of at least one adverse event and sedation).[4] To combine studies, the random effects model was used, which is more conservative than the fixed effects model and produces a wider CI.[4] For dichotomous data, the risk ratio (RR) was estimated with 95% CIs.[4] For continuous outcomes, SMDs were used.[4]

In total, only 3 eszopiclone RCTs were identified, two blinded placebo-controlled (n=60) trials and one open-label acupuncture-controlled trial (n=96).[4] No drugs were identified for other FDA-approved BZRA sedatives.[4] All studies were conducted among adults with schizophrenia.[4] The two eszopiclone placebo-controlled trials were conducted in the USA and were sponsored by the pharmaceutical industry.[4] A 10-week, double-blind placebo-controlled RCT on the augmentation of antipsychotics with eszopiclone versus that of antipsychotics with placebo found that eszopiclone was superior to placebo in improving the Insomnia Severity Index score; however, no difference was observed in the improvement in PANSS scores and other sleep-related outcomes between the groups.[4] Six patients (31.6%) in the eszopiclone group and 3 patients (17.6%) in the placebo group did not complete the study.[4] The most common adverse events in both treatment groups were sedation (eszopiclone = 42.1%, placebo = 41.2%).[4] A one-week, double-blind placebo-controlled RCT on the augmentation of antipsychotics with eszopiclone versus that of antipsychotics with placebo did not find statistically significant differences in sleep-related outcomes and did not evaluate improvement in psychiatric symptoms.[4] Lastly, an 8-week, open-label, Chinese RCT on the augmentation of antipsychotics with eszopiclone versus that of antipsychotics with shallow needling (a form of acupuncture) for the treatment of patients with schizophrenia did not find statistically significant differences in the improvement of PANSS scores and Pittsburgh Sleep Quality Index score between the groups.[4]

Based on the evidence of this review, eszopiclone may be useful for the treatment of insomnia symptoms in patients with schizophrenia, but the overall evidence is mixed and is low quality.[4] Eszopiclone did not improve schizophrenia symptoms in either of the 3 studies.[4] The use of other BZRAs is not advised because they have not been studied in this population.[4]

Risk of Falls and Hip Fractures with Benzodiazepine and Benzodiazepine Receptor Agonist Sedatives

There is a well-established associated between benzodiazepines and fracture risk, but the association of BZRAs (zolpidem, zaleplon and zopiclone) is less clear.[5,6] Two recent systematic reviews have evaluated these associations in more depth: the objectives of one review[5] were to investigate the association between benzodiazepine or BZRA use and hip fracture risk; the second review[6] assessed the association between BZRA use and the risk for fractures, falls and injuries.

Studies in the Donnelly, et al. review were included if all of the following criteria applied: 1) RCT, cohort or case-control study; 2) reported outcome was hip fracture or fragility fracture (within which outcome ≥70% of fractures were hip fractures); 3) patients were prescribed either a benzodiazepine or BZRA, or were

matched as a non-exposed control population; and 4) the study population was at least 50 years of age or older with a mean age over 65 years.[5] Exposure was categorized into two main subgroups: exposure to a benzodiazepine versus non-exposure; and exposure to a BZRA versus non-exposure.[5] Benzodiazepine exposure was defined as patients prescribed diazepam, lorazepam, chlordiazepoxide, oxazepam, temazepam or clobazam.[5] Exposure to BZRA was defined as patients prescribed zaleplon, zolpidem or zopiclone.[5] Length of use was defined from the first prescription date, provided there was at least one preceding hypnotic-free month.[5] Short-term use was defined as up to 14 days, medium-term use was defined as 15 days to 30 days, and long-term use was longer than one month; mixed use was a combination of medium and long-term users.[5] The risk of hip fracture in those exposed to one of these drug classes was compared to patients not taking these medications.[5] The measure of effect was the adjusted relative risk (RR) with the associated 95% CI.[5] Included comparisons were studies of: people using benzodiazepine compared to those not exposed; and people using a BZRA compared to those not exposed.[5] Non-randomized study designs were described narratively and only pooled into a meta-analysis if the investigators determined their context, population, medication (including delivery) were clinically similar.[5] Statistical heterogeneity was summarized using an I^2 statistic.[5] Where I^2 was reported higher than 75%, subgroups were explored to explain the heterogeneity.[5]

No RCTs were identified; overall, 18 studies were included: 9 case control studies and 9 cohort studies.[5] Studies were compared for differences in the context of their setting including of location, design, fracture type, mean age, sample size, length of drug exposure and adjustment for confounders with attention to dose.[5] The included sample sizes ranged from 500 to 906,422 participants.[5] The mean age in the studies ranged from 72.0 to 84.3 years.[5]

Eighteen of the studies assessed the effect of benzodiazepine use compared to non-exposure.[5] There was an associated increase in hip fracture risk with benzodiazepine use (RR 1.52; 95% CI, 1.37 to 1.68; $p<0.001$; $I^2 = 67\%$).[5] Severe heterogeneity was explained by the varying length of use; therefore, the risk of fracture was dependent on the length of use.[5] Short-term use carried a 140% increased risk of hip fracture (RR 2.40; 95% CI, 1.88 to 3.05; $p<0.001$; $I^2 = 27\%$).[5] Medium-term use carried 53% increased risk (RR 1.53; 95% CI, 1.22 to 1.92; $p<0.001$; $I^2 = 0\%$) and long-term use carried 20% increased risk (RR 1.20; 95% CI, 1.08 to 1.34; $p<0.001$; $I^2 = 0\%$).[5] The mixed length of use subgroup carried a 52% increased risk (RR 1.52; 95% CI, 1.35 to 1.71; $p<0.001$; $I^2 = 59\%$), but given the high heterogeneity of this group, the investigators cautioned any interpretations of this finding.[5]

Six of the studies assessed the effect of BZRA use compared to non-exposure.[5] There was an associated increased risk of hip fractures with BZRA use (RR 1.90; 95% CI, 1.68 to 2.13; $p<0.001$; $I^2 = 26\%$).[5] Short-term use carried a 139% increased risk of hip fracture (RR 2.39; 95% CI, 1.74 to 3.29; $p<0.001$; $I^2 = 26\%$).[5] Mixed use carried an 80% increased risk (RR 1.80; 95% CI, 1.60 to 2.02; $p=0.001$; $I^2 = 0\%$).[5]

Studies in the Treves, et al. review were eligible if they evaluated adults (age ≥18 years) who received a BZRA and a control group who were not treated with a BZRA.[6] The control group could include participants treated with other sedatives. Studies were only selected if they reported on fractures, falls or injuries.[6] No restriction was placed on how these outcomes were defined in order to perform a more comprehensive evaluation.[6] The possible impact of variation in terminology and study design was addressed by measuring heterogeneity and utilizing random-effects models and subgroup analyses.[6]

A total of 14 studies, including 5 cohort studies and 9 case-control studies were included in the systematic review.[6] The analysis concerning fractures included 10 studies with 830,877 participants (including 146,678 exposed to a BZRA).[6] A statistically significant increased risk for fractures was found with BZRA use, with evidence of significant heterogeneity (odds ratio [OR] 1.63; 95% CI, 1.42 to 1.87; $I^2 = 90\%$).[6] Estimates obtained from case-control studies were similar to those obtained from cohort studies.[6] When 3 studies contributing most to the heterogeneity were excluded, a similar risk was found, while the heterogeneity decreased (OR 1.52; 95% CI, 1.39 to 1.66; $I^2 = 58\%$, n=191,598 participants).[6] Subgroup analyses did not find any differences in risk of fracture between the BZRA sedatives.[6] When the effect of insomnia was considered as a confounder, a subgroup analysis of studies with control groups diagnosed with insomnia still

resulted in statistically significant increased risk for fractures with BZRA exposure (OR 1.28; 95% CI, 1.08 to 1.53; I^2 = 71%).[6] The analysis concerning falls included 3 studies with 19,505 participants.[6] The BZRAs were not associated with a statistically significant increased risk for falls; however, the trend suggests an increased risk and there was evidence of significant heterogeneity (OR 2.40; 95% CI, 0.92 to 6.27; I^2 = 95%).[6] The analysis concerning injuries included 2 studies with 160,502 participants (78,322 were exposed to zolpidem).[6] A statistically significant increased risk for injuries was also found with BZRA use, with no evidence of heterogeneity (OR 2.05; 95% CI, 1.95 to 2.15; I^2 = 0%).[6]

These systematic reviews found an increase in the association between both benzodiazepine and BZRA use with hip fracture, general fractures, falls and injuries.[5,6] There appears to be little difference in the findings between benzodiazepine and BZRA sedatives.[5,6] The risk of fracture depended on the length of time people used their medication, and newly prescribed users of these drugs were at the greatest risk of hip fracture.[5,6]

After further review, two systematic reviews were excluded due to lack of adequate comparator (e.g. only eligible studies were placebo-controlled trials of a single drug)[16,17] and one systematic review was excuded due to lack of applicability (use of sedatives at high altitudes).[3]

New Guidelines:
High Quality Guidelines:

<u>The American Academy of Sleep Medicine (2017)</u>
The purpose of this guideline was to establish clinical practice recommendations for the pharmacologic treatment of chronic insomnia in adults.[8] The relative benefits of pharmacotherapy to CBT, which is already recognized as the standard of therapy, was not addressed.[8] The guideline task force recognized, however, that despite the favorable benefit to risk ratio of CBT, not all patients with an insomnia disorder can derive benefit from CBT alone.[8] Pharmacotherapy, alone or in combination with CBT, should be considered as a treatment option for insomnia.[8]

The guideline included a systematic review and meta-analyses which provided the basis for the conclusions and recommendations. The GRADE approach (Grades of Recommendation, Assessment, Development and Evaluation) was used for the assessment of quality of evidence. The task force assessed the following 3 factors to determine the direction and strength of a recommendation: quality of evidence, balance of beneficial and harmful effects, and patient values and preferences.[8] First, quality of evidence was based exclusively on the studies that could be included in the meta-analyses. The task force determined their overall confidence that the estimated effect found in the studies was representative of the true treatment effect that patients would see, based on the following criteria: overall risk of bias (randomization, blinding, allocation concealment, selective reporting, and author disclosures); imprecision (when 95% CI crosses the clinical significance threshold); inconsistency (I^2 cutoff of 75%); indirectness (study population); and risk of publication bias (funding sources).[8] Second, the task force determined if the beneficial outcomes of the intervention outweighed any harmful adverse effects based on what was reported in the studies and the clinical expertise of the task force.[8] Thirdly, the task force determined if patient values and preferences would be generally consistent, and if patients would use the intervention based on the body of evidence reviewed.[8]

Taking these major factors into consideration and adhering to GRADE recommendations, the task force assigned a direction (for or against) and strength (strong or weak) for each recommendation statement.[8] Additional contextual remarks were provided with each recommendation, which were based on the evidence evaluated during the systematic review.[8]

A STRONG recommendation is one that clinicians should, under most circumstances, always be following when pharmacological treatment is indicated (i.e., something that might qualify as a quality measure).[8] A WEAK recommendation reflects a lower degree of certainty in the appropriateness of the patient-care strategy and requires that the clinician use their clinical knowledge and experience, and refer to the individual patient's values and preferences to determine the best course of action.[8]

This guideline made two major recommendations. The first recommendation is that all patients with chronic insomnia should receive CBT as the initial and primary intervention.[8] They graded this recommendation as a strong recommendation based on moderate-quality evidence.[8] The second recommendation is that a shared decision-making approach be employed by clinicians in determining whether pharmacotherapy should be initiated for those patients who do not achieve adequate response with CBT.[8] This second major recommendation was graded as a weak recommendation based on low quality evidence.[8]

The systematic review found that very few comparative efficacy studies have been conducted among these agents so the guideline provides a recommendation and evidence base for each individual drug as summarized in **Table 5**.[8]

Table 5. Summary of Clinical Practice Recommendations for Adults with Chronic Insomnia (Adapted from the American Academy of Sleep Medicine).[8]

Treatment	Recommendation	Strength of Recommendation	Quality of Evidence	Benefits and Harms Assessment	Summary of Clinically Meaningful Outcomes
Orexin Receptor Agonists					
Suvorexant *Based on 10, 15, 20 mg doses*	Suvorexant is suggested as a treatment for sleep maintenance insomnia (versus no treatment).	WEAK	LOW	Benefits outweigh harms	Efficacy: Total sleep time: Mean improvement was 10 min longer, compared to placebo (95% CI: 2 to 19 min improvement); Wake after sleep onset: Mean reduction was 16–28 min greater vs. placebo (95% CI: 7 to 43 min reduction); Quality of sleep: Not reported. Harm: Overall frequency of adverse events not significantly increased vs. placebo. No evidence of daytime residual or withdrawal symptoms.
Benzodiazepine Receptor Agonists					
Eszopiclone *Based on 2, 3 mg doses*	Eszopiclone is suggested as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment).	WEAK	VERY LOW	Benefits outweigh harms	Efficacy: Sleep latency: Mean reduction was 14 min greater vs. placebo (95% CI: 3 to 24 min reduction); Total sleep time: Mean improvement was 28–57 min longer vs. placebo (95% CI: 18 to 76 min improvement); Wake after sleep onset: Mean reduction was 10 –14 min greater vs. placebo (95% CI: 2 to 18 min reduction); Quality of sleep*: Moderate-to-large improvement vs. placebo. Harm: Limited or no consistent evidence of adverse events in excess of placebo, with possible exception of unpleasant taste.
Zaleplon *Based on 10 mg dose*	Zaleplon is suggested as a treatment for sleep onset	WEAK	LOW	Benefits outweigh harms	Efficacy: Sleep latency: Mean reduction was 10 min greater vs. placebo (95% CI: 0 to 19 min reduction);

	insomnia (versus no treatment).				Quality of sleep*: No improvement in quality of sleep vs. placebo. Harm: No statistical evidence of adverse events in excess of placebo, but some treatment-emergent adverse events were numerically more prevalent than placebo.
Zolpidem *Based on 10 mg dose*	Zolpidem is suggested as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment).	WEAK	VERY LOW	Benefits outweigh harms	Efficacy: Sleep latency: Mean reduction was 5-12 min greater vs. placebo (95% CI: 0 to 19 min reduction); Total sleep time: Mean improvement was 29 min longer vs. placebo (95% CI: 11 to 47 min improvement); Wake after sleep onset: Mean reduction was 25 min greater vs. placebo (95% CI: 18 to 33 min reduction); Quality of sleep*: Moderate improvement in quality of sleep vs. placebo. Harm: Limited evidence of mild adverse events in excess of placebo, with the possible exception of excessive sleepiness following administration of higher doses (10 mg) less than 8 hours prior to awakening.
Benzodiazepines					
Triazolam *Based on 0.25 mg dose*	Triazolam is suggested as a treatment for sleep onset insomnia (versus no treatment).	WEAK	HIGH	Benefits approximately equal to harms	Efficacy: Sleep latency*: Mean reduction was 9 min greater, compared to placebo (95% CI: 4 to 22 min reduction); Quality of sleep*: Moderate improvement vs. placebo. Harm: Insufficient data available for meta-analyses. Speech disorder was significantly more frequent than placebo in one report.
Temazepam *Based on 15 mg dose*	Temazepam is suggested as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment).	WEAK	MODERATE	Benefits outweigh harms	Efficacy: Sleep latency: Mean reduction was 37 min greater vs. placebo (95% CI: 21 to 53 min reduction); Total sleep time: Mean improvement was 99 min longer vs. placebo (95% CI: 63 to 135 min improvement); Wake after sleep onset: Not reported; Quality of sleep*: Small improvement vs. placebo. Harm: Insufficient data available for meta-analyses. Limited or no consistent evidence of adverse events in excess of placebo but daytime impairment has been noted.
Melatonin agonists					
Ramelteon *8 mg dose*	Ramelteon is suggested as a treatment for sleep onset insomnia (versus no treatment).	WEAK	VERY LOW	Benefits outweigh harms	Efficacy: Sleep latency: Mean reduction was 9 min greater vs. placebo (95% CI: 6 to 12 min reduction); Quality of sleep*: No improvement vs. placebo. Harm:

					Relatively low frequency of adverse effects overall and none which were significantly different than placebo.
Heterocyclics					
Doxepin *3, 6 mg doses*	Doxepin is suggested as a treatment for sleep maintenance insomnia (versus no treatment).	WEAK	LOW	Benefits outweigh harms	Efficacy: Total sleep time: Mean improvement was 26–32 min longer vs. placebo (95% CI: 18 to 40 min improvement); Wake after sleep onset: Mean reduction was 22–23 min greater vs. placebo (95% CI: 14 to 30 min reduction); Quality of sleep*: Small-to-moderate improvement vs. placebo. Harms: Minimal evidence of adverse events in excess of placebo.
Trazodone *50 mg dose*	Trazodone is **not recommended** as treatment for sleep onset or sleep maintenance insomnia (versus no treatment). This recommendation is based on the perception of trazodone as a "safer" sleep-promoting agent by many physicians despite absence of significant efficacy and paucity of information regarding harms.	WEAK	MODERATE	Harms outweigh benefits	Efficacy: Sleep latency*: Mean reduction was 10 min greater vs. placebo (95% CI: 9 to 11 min reduction); Wake after sleep onset: Mean reduction was 8 min greater vs. placebo (95% CI: 7 to 9 min reduction); Quality of sleep*: No improvement in quality of sleep vs. placebo Harms: Trazodone associated with significantly more adverse events vs. placebo, mostly headache and somnolence (based on one trial)
Over-the-Counter Products					
Diphenhydramine *50 mg dose*	Diphenhydramine is **not recommended** as treatment for sleep onset or sleep maintenance insomnia (versus no treatment). This recommendation is based on the absence of evidence for clinically significant improvement.	WEAK	LOW	Benefits approximately equal to harms	Efficacy: Sleep latency: Mean reduction was 8 min greater vs. placebo (95% CI: 2 min increase to 17 min reduction); Total sleep time: Mean improvement was 12 min longer vs. (95% CI: 13 min reduction to 38 min improvement); Quality of sleep*: No improvement vs. placebo. Harms: No meta-analyses of adverse effects possible with minimal evidence of adverse events in excess of placebo.
Melatonin *2 mg dose*	Melatonin is **not recommended** as treatment for sleep onset or sleep maintenance insomnia (versus no treatment). This recommendation is based on its availability and the widespread perception of melatonin as a benign sleep aid despite paucity of evidence for the 2 mg dose in adults.	WEAK	VERY LOW	Benefits approximately equal to harms	Efficacy: Sleep latency: Mean reduction was 9 min greater vs. placebo (95% CI: 2 to 15 min reduction); Quality of sleep*: Small improvement vs. placebo. Harms: No meta-analyses of adverse effects possible with minimal evidence of adverse events in excess of placebo.

Note: All reported measures are based on polysomnographic data, unless otherwise noted.
*Based on subjective reporting

Using the GRADE approach, quality of evidence for randomized clinical trials began at HIGH and were downgraded progressively for heterogeneity, imprecision or potential publication bias.[8] Therefore, since most studies were industry-sponsored, the quality of evidence for nearly all of them was reduced from HIGH to MODERATE.[8] The extent to which this downgrading of evidence is warranted due to actual publication bias is unknown, but under the GRADE system the task force chose to adopt a conservative approach and assume risk of bias.[8] When heterogeneity and imprecision were accounted for, the quality of evidence for many treatments considered was LOW or VERY LOW.[8] Heterogeneity and imprecision are not uncommon for these studies due to substantial variability in sleep outcome variables across studies and confidence intervals that frequently overlap the clinical thresholds for significance.[8] Thus, the recommendations were graded as WEAK, in that they are based on relatively limited and low quality evidence.[8]

Most medications included in the meta-analyses are FDA-approved drugs for treatment of insomnia.[8] The task force was aware that FDA approval rests on the demonstration of *statistically* significant changes in both subjective and objective outcomes.[8] The task force recognized that many agents have been shown in one or more studies to be *statistically significantly superior* to placebo for a given outcome, but are nonetheless not recommended for treatment of chronic insomnia in this guideline.[8] The task force emphasized the importance of understanding the discrepancy which results from different criteria employed by the FDA and individual studies versus GRADE.[8] The GRADE approach establishes evidence quality ratings and *clinical* significance thresholds that are not employed in individual clinical trials and FDA assessment for approval.[8]

The task force also noted that it is important for clinicians to understand that a recommendation against use, particularly when associated with low quality evidence, is not equivalent to a demonstration of ineffectiveness.[8] Rather, it is often an indication that the available evidence is insufficient and fails to provide convincing support in favor of use by GRADE standards.[8]

Of note, tasimelteon (a melatonin agonist), doxylamine (an over-the-counter antihistamine) and midazolam (a benzodiazepine) were not included in the guideline, although these drugs are included in the OSHP FFS PDL sedative drug class.

<u>The European Sleep Research Society (2017)</u>
This European guideline for the diagnosis and treatment of insomnia was developed to provide clinical recommendations for the management of adult patients with insomnia for physicians and clinical psychologists who diagnose and treat patients with insomnia, including insomnia co-morbid with somatic or mental disorders.[9] The guideline is based on a systematic review of relevant meta-analyses from 1966 to 2016.[9] The GRADE approach was used for the assessment of quality of evidence and to inform recommendations.[9] The published evidence was rated as high quality if the examined meta-analyses suggested it to be very unlikely that further research would change the guideline task force's confidence in the estimate of effect.[9] In contrast, evidence was rated as low quality when the meta-analyses suggested that any estimate of effect was uncertain.[9] Two grades of recommendations were used: 'strong' and 'weak'.[9] Recommendation grades were based on a consensus between members of the guideline task force from the body and quality of evidence.[9]

The grading of recommendations from the guideline are summarized in **Table 6**.

Table 6. Recommendations from the European Sleep Research Society.[9]

Diagnostic management of insomnia and its co-morbidities

- Diagnostic procedure for insomnia should include an evaluation of the current sleep–wake behavior, sleep history, somatic and mental disorders, a physical examination, the use of sleep questionnaires and sleep diaries, and additional tests, if indicated (blood test, ECG, EEG, CT/MRT, circadian markers). (**strong recommendation, moderate- to high-quality evidence**).
- The clinician should ask for medication and other substance use (alcohol, caffeine, nicotine, illegal drugs), which may disturb sleep (**strong recommendation, high-quality evidence**).
- Sleep diaries or actigraphy can be used in case of clinical suspicion of irregular sleep–wake schedules or circadian rhythm disorders (**strong recommendation, high-quality evidence**), and actigraphy can be used to assess quantitative sleep parameters (**weak recommendation, high-quality evidence**).
- Polysomnography is recommended when there is clinical suspicion of other sleep disorders, like periodic limb movement disorder, sleep apnea or narcolepsy, treatment-resistant insomnia, insomnia in occupational at-risk groups, or suspicion of a large discrepancy between subjectively experienced and polysomnographically measured sleep (**strong recommendation, high-quality evidence**).

Treatment of Insomnia

In the presence of co-morbidities, clinical judgement should guide whether insomnia or the co-morbid condition is treated first, or whether both are treated at the same time.

CBT

- CBT is recommended as first-line treatment for chronic insomnia in adults of any age (**strong recommendation, high-quality evidence**).
- A pharmacological intervention can be offered if CBT is not effective or not available.

BZD and BZRA

- BZDs and BZRAs are effective in the short-term treatment of insomnia (≤4 weeks; **high-quality evidence**).
- The newer BZRAs are equally effective as BZDs (**moderate-quality evidence**).
- BZDs or BZRAs with shorter half-lives may have less adverse effects concerning sedation in the morning (**moderate-quality evidence**).
- Long-term treatment of insomnia with a BZD or BZRA is not generally recommended because of a lack of evidence and possible adverse effects (**strong recommendation, low-quality evidence**). In patients using medication on a daily basis, reduction to intermittent dosing is strongly recommended (**strong recommendation, low-quality evidence**).

Sedating Antidepressants

- Sedating antidepressants are effective for short-term treatment of insomnia; contraindications have to be carefully considered (**moderate-quality evidence**). Long-term treatment of insomnia with sedating antidepressants is not generally recommended because of a lack of evidence and possible adverse effects (**strong recommendation, low-quality evidence**).

Antihistamines

- Because of insufficient evidence, antihistamines are not recommended for insomnia treatment (**strong recommendation, low-quality evidence**).

Antipsychotics

- Because of insufficient evidence and in light of their adverse effects, antipsychotics are not recommended for insomnia treatment (**strong recommendation, very low-quality evidence**).

Melatonin

- Melatonin is not generally recommended for the treatment of insomnia because of limited efficacy (**weak recommendation, low-quality evidence**).

Phytotherapy

- Valerian and other phytotherapeutics are not recommended for the treatment of insomnia because of poor evidence (**weak recommendation, low-quality evidence**).

Light therapy and exercise

- Light therapy and exercise regimes may be useful as adjunct therapies (**weak recommendation, low-quality evidence**).

Complementary and alternative medicine

- Acupuncture, aromatherapy, foot reflexology, homeopathy, meditative movement, moxibustion and yoga are not recommended for the treatment of insomnia because of poor evidence (**weak recommendation, very low-quality evidence**).

Abbreviations: BZD = benzodiazepine; BZRA = benzodiazepine receptor agonist; CBT = cognitive behavioral therapy for insomnia; CT = Computed Tomography; ECG = electrocardiogram; EEG = electroencephalogram; MRT = Magnetic Resonance Tomography.

Additional Guidelines for Clinical Context:
No other new guidelines were identified.

New Formulations or Indications:
No new formulations or indications identified.

New FDA Safety Alerts:

Table 7. Description of New FDA Safety Alerts[10,18]

Generic Name	Trade Name	Month / Year of Label Change	Location of Labeling Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Eszopiclone	LUNESTA	8/2019	**Boxed Warning**	**COMPLEX SLEEP BEHAVIORS including sleepwalking, sleep-driving, and engaging in other activities while not fully awake may occur following use of eszopiclone. Some of these events may result in serious injuries, including death. Eszopiclone must be discontinued immediately if a patient experiences a complex sleep behavior.**
Zaleplon	SONATA	8/2019	**Boxed Warning**	**COMPLEX SLEEP BEHAVIORS including sleepwalking, sleep-driving, and engaging in other activities while not fully awake may occur following use of zaleplon. Some of these events may result in serious injuries, including death. Zaleplon must be discontinued immediately if a patient experiences a complex sleep behavior.**
			Warnings and Precautions	Use in Patients with Depression: In primarily depressed patients treated with sedative-hypnotics, worsening of depression, including suicidal thoughts and actions (including completed suicides), have been reported.
		2/2019	Warnings and Precautions	Because zaleplon can cause drowsiness, patients, particularly the elderly, are at higher risk of falls.
Zolpidem	AMBIEN; AMBIEN CR; EDLUAR; INTERMEZZO	8/2019	**Boxed Warning**	**COMPLEX SLEEP BEHAVIORS including sleepwalking, sleep-driving, and engaging in other activities while not fully awake may occur following use of zolpidem. Some of these events may result in serious injuries, including death. Zolpidem must be**

				discontinued immediately if a patient experiences a complex sleep behavior.
Suvorexant	BELSOMRA	3/2020	Warnings and Precautions	Use in Patients with Depression: • In primarily depressed patients treated with sedative-hypnotics, worsening of depression, including suicidal thoughts and actions (including completed suicides), have been reported.
		2/2019	Warnings and Precautions	• Because zaleplon can cause drowsiness, patients, particularly the elderly, are at higher risk of falls.
ALL BENZODIAZEPINES Alprazolam Chlordiazepoxide Clobazam Clonazepam Clorazepate Diazepam Estazolam Flurazepam Lorazepam Oxazepam Quazepam Temazepam Triazolam		9/2020	**Boxed Warning**	**To address the serious risks of abuse, addiction, physical dependence, and withdrawal reactions:** **The Boxed Warning will be updated to the prescribing information for all benzodiazepines. This information will describe the risks of abuse, misuse, addiction, physical dependence, and withdrawal reactions consistently across all the medicines in the class. Other changes are also being required to several sections of the prescribing information, including to the Warnings and Precautions, Drug Abuse and Dependence, and Patient Counseling Information sections.**
Triazolam	HALCION	10/2019	Contraindications	• Patients with known hypersensitivity to triazolam, any of component of triazolam, or other benzodiazepines. • Reactions consistent with angioedema (involving the tongue, glottis, or larynx), dyspnea, and throat closing have been reported and may be fatal. • Concomitant administration of strong cytochrome P450 (CYP 3A) enzyme inhibitors (e.g., ketoconazole, itraconazole, nefazodone, lopinavir, ritonavir).
		10/2019	Adverse Reactions	Post-marketing Experience: • General disorders and administration site conditions: Paradoxical drug reaction, chest pain and fatigue • Gastrointestinal disorders: Tongue discomfort, glossitis, stomatitis • Hepatobiliary disorders: Jaundice • Injury, poisoning and procedural complications: Falls • Psychiatric disorders: Confusional state (disorientation, derealization, depersonalization), mania, agitation, restlessness, irritability, sleep disorder and libido disorder,

				hallucination, delusion, aggression, somnambulism, and abnormal behavior
		2/2019	Warnings and Precautions	• Because triazolam can cause drowsiness, patients, particularly the elderly, are at higher risk of falls. • Advise patients that increased drowsiness and decreased consciousness may increase the risk of falls in some patients.
		12/2016	**Boxed Warning**	**WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS** **Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death.** • **Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.** • **Limit dosages and durations to the minimum required.** • **Follow patients for signs and symptoms of respiratory depression and sedation.**

Randomized Controlled Trials:

A total of 290 citations were manually reviewed from the initial literature search. After further review, all but 3 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 table below. Full abstracts are included in **Appendix 2**.

Table 8. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Hanna, et al.[19] SC DB RCT N=80	Midazolam syrup 0.5 mg/kg PO Zolpidem solution 0.25 mg/kg PO	Children 2-9 y undergoing elective inpatient procedure ≥2 h duration	Anxiety, measured by the modified Preoperative Anxiety Scale (mYPAS) at time of separation from parents	Midazolam: 26.7 Zolpidem: 30.0 Difference: NS Conclusion: No statistically significant difference in anxiety could be found between oral midazolam and zolpidem at time of surgery.
Impellizzeri, et al.[20] SC DB RCT N=80	Midazolam syrup 0.5 mg/kg PO Melatonin solution 0.5 mg/kg PO	Children 8-14 y undergoing elective inpatient procedure	Anxiety, measured by the mYPAS) in preoperative room	Midazolam: 38.8 Melatonin: 36.3 Difference: NS Conclusion: No statistically significant difference in anxiety could be found between oral midazolam and melatonin at time of surgery.
Yu, et al.[21] SC DB PC PG RCT	Zolpidem 10 mg PO QHS + paroxetine 20 mg PO QAM	Adults with primary insomnia disorder	Change in PSG-defined SE (sleep time/time in bed × 100%), TST, SOL, and WASO	Zolpidem + paroxetine: SE = +18.3% ($p<0.05$ vs. control) SOL = -14.9 minutes ($p=0.199$ vs. control) WASO = -75.2 minutes ($p<0.05$ vs. control)

N=78	Zolpidem 10 mg PO QHS + placebo PO QAM		(baseline night and the night in week 8.	TST = +90.9 minutes (p<0.05 vs. control) Zolpidem + placebo: SE = +12.1% SOL = -14.2 minutes WASO = -44.7 minutes TST = +60.1 minutes Conclusion: zolpidem plus paroxetine improves sleep maintenance, but not sleep onset, compared to zolpidem alone in patients with primary insomnia.

Abbreviations: DB = double blind; PO = orally; NS = not statistically significant; PC = placebo controlled; PG = parallel group; PSG = polysomnography; QAM = each morning; QHS = each bedtime; RCT = randomized controlled trial; SC = single-centered; SE = sleep efficiency; SOL = sleep onset latency; TST = total sleep time; WASO = week after sleep onset; y = years.

NEW DRUG EVALUATION:

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

Clinical Efficacy:

Lemborexant, an orexin receptor antagonist similar to suvorexant, was approved by the FDA in December 2019 for the treatment of adults with insomnia, characterized by sleep onset or sleep maintenance.[11] The pharmacology and pharmacokinetic properties of lemborexant are summarized in **Table 9**.

Table 9. Pharmacology and Pharmacokinetic Properties of Lemborexant.[11]

Parameter	
Mechanism of Action	Reversible competitive antagonist at orexin receptors 1 and 2 (greater affinity for orexin receptor 2). The orexin neuropeptide signaling system plays a role in wakefulness and blocking the orexin receptors is thought to suppress wake drive.
Oral Bioavailability	T_{max} = 1-3 hours High-fat, high calorie meal decreased C_{max} by 24%, AUC increased by 185 and Tmax was delayed by ~2 hours.
Distribution and Protein Binding	V_d = 1970 L Protein binding = 94% *in vitro*
Elimination	57.4% of the dose is recovered in the feces and 29.1% in the urine (<1% unchanged).
Half-Life	5 mg = 17 hours; 10 mg = 19 hours
Metabolism	Primarily metabolized by CYP3A4

Abbreviations: AUC = area under the curve; C_{max} = peak concentration; L = liters; T_{max} = time to peak concentration; V_d = volume of distribution.

Two Phase 3 clinical trials evaluated the efficacy and safety of lemborexant.[12,13] Both studies were randomized, double-blind, parallel-group, placebo-controlled, studies sponsored by Eisai Inc.[12,13] Study sites were primarily conducted in North America, Europe and Asia. Key participant inclusion and exclusion criteria for both studies were similar and are summarized in **Table 10**. Both trials required eligible participants to have a diagnosis of insomnia disorder based on *Diagnostic and Statistical Manual of Mental Disorders (5th Ed)* DSM-5 criteria; subjective wake-after-sleep onset (sWASO), defined as the estimated sum of time of wake during the night after initial sleep onset until the participant got out of bed for the day, for 60 minutes or longer at least 3 times per week; and a score 13 or higher,[12] or 15 or higher,[13] on the ISI. After the initial screening periods in both trials, eligible patients received placebo for a 2-week run-in period to rule out placebo responders and to identify patients who did not adhere to sleep diary instructions. A summary of the populations studied in both trials can be found in **Table 10**.

The first trial was a 30-day study that evaluated lemborexant in older adults against placebo and zolpidem ER.[12] Older adults tend to have relatively more difficulty maintaining sleep, yet sedative hypnotics used in this population increase risk of adverse events, such as falls, hip fractures, and other injury.[5,6] The investigators wanted to determine how lemborexant, a dual orexin receptor antagonist, would compare with placebo and a long-acting BZRA. Efficacy outcomes included change from baseline in objective sleep onset and sleep maintenance at the beginning and end of treatment to 30 days, measured by PSG and averaged between days 1 and 2 and between days 29 and 30.[12] The primary efficacy endpoint was change in LPS as measured by PSG, defined as minutes from lights off to the first 10-minute consecutive period of nonwakefulness after 1 month of treatment.[12] Key secondary endpoints included sleep maintenance outcomes of sleep efficiency (proportion of time spent asleep per time in bed, calculated as TST/interval from lights off to lights on [standardized at 8 hours]), WASO, and WASO in the second half of the night (WASO2H; minutes awake from 240 minutes after lights off until lights on).[12] For primary endpoint comparison, LPS is known to be nonnormally distributed, so a log transformation was used in the LPS analysis, and statistical comparisons were made based on least squares geometric mean (LSGM) treatment ratios.[12]

At 30 days, the decrease from baseline in LPS as measured by PSG was larger and statistically significant for both lemborexant 5 mg and 10 mg doses compared to placebo and zolpidem ER (see **Table 10**).[12] These statistically significant differences were observed immediately on days 1 and 2, and throughout the 30-day treatment period. Key secondary endpoints, which objectively measured sleep maintenance outcomes by PSG, also resulted in statistically significant differences between lemborexant 5 mg and 10 mg compared to placebo and zolpidem ER (see **Table 10**).[12] Statistically significant differences for secondary endpoints were also observed immediately on days 1 and 2, and throughout the 30-day treatment period.[12]

The second trial was a 6-month placebo-controlled study with a 6-month extension in which all participants either continued lemborexant or were switched from placebo to lemborexant.[13] Sleep onset and sleep maintenance endpoints were analyzed using data from electronic sleep diaries completed daily by each study participant.[13] The primary efficacy endpoint was subjective sleep onset latency (sSOL), a sleep onset outcome.[13] Key secondary endpoints evaluated sleep maintenance as measured by sWASO, subjective total sleep time (sTST), defined subjectively as the total time spent asleep during their time in bed, and subjective sleep efficiency (sSE), which was expressed as the proportion of sTST per subjective time in bed.[13]

At 6 months, the decrease from baseline in sSOL was larger and statistically significant (also assessed by the LSGM treatment ratio) for both lemborexant 5 mg and 10 mg doses compared to placebo (see **Table 10**).[13] These differences were observed during the first week of treatment, and throughout the 6-month treatment period. Key secondary endpoints, which measured subjective sleep maintenance outcomes, also resulted in statistically significant differences between lemborexant 5 mg and 10 mg compared to placebo (see **Table 10**).[13]

Several limitations should be noted. Risk of bias and applicability assessments for both trials can be found in **Table 10**. In summary, both trials limited selection bias through the randomization process. Performance bias was also limited by blinding patients and all personnel involved with the conduct and interpretation of the studies. The 30-day trial[12] described a double-dummy design while the 6-month trial[13] did not provide an adequate description of how blinding of treatment groups was assured. A true intention-to-treat analysis was also not performed which is important, especially when there is high attrition early in the study as observed in the 6-month trial.[13] Rather, data analysis was limited to patients who had received at least one dose of study drug and had at least one post-dose primary efficacy measurement.[12,13] Risk for attrition bias was high with the 6-month trial because of the overall high attrition (>20%) in all treatment arms.[13] For the primary endpoint comparisons, it is also important to note that the clinical context of endpoints expressed as LSGMs can be difficult to interpret.[12,13] In addition, both trials were funded by the drug sponsor (Eisai Inc.), who participated in the design and conduct of the studies; who were involved in data collection, data management, data analysis, and data interpretation; and who were involved in the preparation, review, and approval of the manuscript for publication.[12,13]

Clinical Safety:

In the 6-month trial, drug exposure was similar across treatment groups, with 82.1%, 79.9%, and 73.9% of participants having at least 6 months of exposure for placebo, lemborexant 5 mg, and lemborexant 10 mg, respectively.[13] A similar incidence of TEAEs was observed across both lemborexant doses and placebo treatment groups, with most of the TEAEs mild or moderate in severity.[13] The most common TEAE was somnolence, which was reported in 1.6%, 8.6% and 13.1% of patients in the placebo, lemborexant 5 mg and lemborexant 10 mg treatment arms, respectively.[13] The incidence of serious and severe TEAEs was low and similar across all treatment arms.[13] More patients in the lemborexant 10 mg group (8.3%) discontinued the study early due to a TEAE compared with the 5 mg (4.1%) or placebo (3.8%) groups.[13] The most common TEAE leading to study drug discontinuation was somnolence (placebo = 0.6%, lemborexant 5 mg = 1.0%, lemborexant 10 mg = 2.9%).[13] The investigators could not find any correlation between baseline characteristics, including age, sex, race, ethnicity, region, and country, and participants who discontinued study treatment early due to somnolence.[13]

In the 30-day trial, the long-term safety of lemborexant therapy could not be evaluated.[12] The overall incidence of TEAEs was similar among treatment groups.[12] Six patients reported 8 serious adverse events (4 in zolpidem ER group; 2 in lemborexant 5 mg group) but none were deemed to be treatment-related.[12] Falls (with or without injury) were reported as a TEAE by 4 patients treated in the lemborexant 5 mg group.[12] Sleep paralysis was reported by 1 patient in the lemborexant 5 mg group and 3 patients in the lemborexant 10 mg group but were deemed mild in severity.[12]

In both trials, no deaths occurred, no complex sleep-related behaviors were reported, no evidence of suicidal ideation, suicidal behavior or self-injury was observed, and no clinically meaningful changes in clinical laboratory tests, vital signs, weight, or electrocardiograms were found.[12,13] Overall mean values for these parameters were within normal range and dose-related trends were not observed.[12,13] In addition, no evidence of withdrawal was found.[12,13]

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Quality of life
2) Daytime Function
3) Sleep onset and maintenance
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoints:

1) Change in LPS (sleep onset outcome)
2) Change in subjective SOL (sleep onset outcome)

Table 10. Comparative Evidence Table for Lemborexant.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
NCT02783729[12,22] DB, PG, PC, AC, RCT Eisai Inc.	1. LEM 5 mg PO QHS 2. LEM 10 mg PO QHS 3. ZOL ER 6.25 mg PO QHS 4. PBO Ratio: 5:5:5:4 Duration: 30 days	Demographics: Age: 63 y (median) Female: 86.4% White: 72.3% Black: 25.4% LPS: 44.5 min WASO: 113.7 min Sleep efficiency: 68.3% Key Inclusion Criteria: -Women ≥55 y -Men ≥65 y -DSM-5 criteria for insomnia disorder* -H/o sWASO ≥60 min for ≥3 nights/wk in past 4 wk -Reports 7-9 h spent in bed sleeping or trying to sleep -Reports habitual bedtime and waketime -Evidence of sleep maintenance insomnia -ISI score ≥13 Key Exclusion Criteria: -Sleep *onset* difficulties only complaint -Concurrent sleep-related breathing disorder (w/ or w/o CPAP tx); periodic limb movement disorder; RLS; circadian rhythm sleep disorder; narcolepsy. -Parasomnia (h/o sleep-eating, sleep-related violence, sleep-driving) based on the MUPS	ITT: 1. 266 2. 269 3. 263 4. 208 PP: 1. 258 2. 260 3. 246 4. 198 Attrition: 1. 3.0% 2. 3.3% 3. 6.5% 4. 4.8%	Primary Endpoint: Δ LPS from Baseline to Nights 29, 30: 1. -19.5 min (SD 33.1) 2. -21.5 min (SD 32.4) 3. -7.5 min (SD 35.1) 4. -7.9 min (SD 32.0) LSGM Tx Ratio vs. PBO: 1. 0.63 (95% CI, 0.56 to 0.72) p<0.001 2. 0.59 (95% CI, 0.52 to 0.68) p<0.001 3. 1.22 (05% CI, 1.06 to 1.40) p=0.006 LSGM Tx Ratio vs. ZOL: 1. 0.63 (95% CI, 0.56 to 0.72) p<0.001 2. 0.59 (95% CI, 0.52 to 0.68) p<0.001 Secondary Endpoints: Δ Proportion of Time Spent in Bed from baseline to Nights 29, 30 (total sleep time/interval from lights off until lights on [standardized at 8 hrs]): 1. 12.9% 2. 14.1% 3. 9.1% 4. 5.4% LSMD vs. PB0: 1. 7.1% (95% CI, 5.6 to 8.5) p<0.001 2. 8.0% (95% CI, 6.6 to 9.5) p<0.001 3. 3.2% (95% CI, 1.7 to 4.6) p<0.001	NA NA NA NA NA NA	Early Discontinuation from TEAE: 1. 0.8% 2. 1.1% 3. 2.3% 4. 1.0% TEAE: 1. 27.8% 2. 30.6% 3. 35.4% 4. 25.4% SAE: 1. 0.8% 2. 0 3. 1.5% 4. 0 Headache: 1. 6.4% 2. 4.9% 3. 5.3% 4. 6.2% Somnolence: 1. 4.1% 2. 7.1% 3. 1.5% 4. 1.9% Falls (n): 1. 4 2. 0 3. 0 4. 0 Sleep Paralysis: 1. 1 2. 3 3. 0	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) computer-generated randomization performed centrally by an interactive voice and web response system. Randomization was stratified by age group (55-65 y vs. ≥65 y). Performance Bias: (low) after 2-week placebo run-in period and randomization, patients and all personnel involved with the conduct and interpretation of the study were blinded to the treatment codes using a double-dummy design. Randomization data were kept strictly confidential, filed securely until time of unblinding. Detection Bias: (unclear) Unknown if data assessors blinded to treatment allocation; outcomes assessed by PSG using avg data from nights 1 and 2 and avg data from night 29 and 30. Efficacy analyses conducted on patients who received 1 dose of randomized drug (mITT). Attrition Bias: (low) Data missing for 3.5% of patients, most of whom withdrew from study early. Missing data generally balanced across treatment groups. Missing data imputed using pattern-mixture model multiple imputation (assumes missing data similar to study completers in respective treatment group). Reporting Bias: (high) drug sponsor (Eisai Inc.) participated in the design and conduct of the study; data collection, data management, data analysis, and data interpretation; preparation, review, and approval of the manuscript; and the decision to submit the manuscript for publication. For primary endpoint comparisons, LPS is known to be nonnormally distributed, so a log transformation was used in the LPS analysis, and statistical comparisons were made based on LSGMs which can be difficult to interpret.

		-AHI >15 episodes/hr as measured by PSG -PLMI >15 episodes/hr as measured by PSG -Depression (BDI-II score >19) -Anxiety (BAI score >15) -Habitually naps 3x/day -Female of child-bearing potential -H/o drug or alcohol dependency in past 2 y -Excessive caffeine use (subjective) -HIV, HepC, HepB -QTc >450 ms -Evidence of clinically significant disease (cardiac, respiratory, renal, psychiatric, malignancy, chronic pain, etc.) -Comorbid nocturia -Any concomitant tx for insomnia, including sedative, OTC drug, marijuana, or CBT		LSMD vs. ZOL: 1. 3.9% (95% CI, 2.5 to 5.3) p<0.001 2. 4.9% (95% CI, 3.5 to 6.3) p<0.001 Δ Minutes of Wake from LPS until Lights On (WASO) from Baseline to Nights 29, 30: 1. -43.9 min (SD 39.3) 2. -46.4 min (SD 39.6) 3. -36.5 min (SD 43.4) 4. -18.6 min (SD 41.9) LSMD vs. PBO: 1. -24.0 min (95% CI, -30.0 to -18.0) p<0.001 2. -25.4 min (95% CI, -31.4 to -19.3) p<0.001 3. -16.3 min (95% CI, -22.3 to -10.2) p<0.001 LSMD vs. ZOL: 1. -7.7 min (95% CI, -13.4 to -2.1) p=0.007 2. -9.1 min (95% CI, -14.8 to -3.5) p=0.002	NA NA NA NA NA NA NA	4. 0		Other Bias: (high) Study funded by Eisai Inc. Data analyzed by statisticians employed by Eisai Inc. **Applicability**: Patient: Study limited to patients at least 55 years of age. Patients with comorbid conditions were excluded. Patients reciving first-line CBT excluded. Mostly white females studied; inclusion criteria confirmed by sleep history, sleep diary and PSG (WASO mean ≥60 min on 2 consecutive PSGs, with neither night <45 min). Intervention: New drug studied to establish efficacy and short-term safety for FDA approval. Patients allocated to the 5 mg arm were not permitted to titrate to 10 mg if the 5 mg dose was ineffective, which conflicts with current prescribing information.[11] Comparator: PBO used to establish efficacy; ZOL ER provides an active comparison, though suvorexant would have provided comparison against the only other Orexin Receptor Antagonist. Outcomes: Primary endpoint assessed sleep initiation and secondary endpoints assessed sleep maintenance. Setting: 67 outpatient sites in Europe and North America.
NCT02952820[13,22] MC, DB, PG, PC, RCT Eisai Inc.	1. LEM 5 mg PO QHS 2. LEM 10 mg PO QHS 3. PBO PO QHS 1:1:1 Duration: 6 months; additional 6-month DL extension for LEM (at same	Demographics: Mean age: 54.5 y Age <65 y: 72.4% Female: 68.2% White: 71.5% Black: 8.0% Japanese: 17.0% Mean BMI: 27.3 Mean ISI: 19.2 Key Inclusion Criteria: -Age ≥18 y -DSM-5 criteria for insomnia disorder* -Confirmation of insomnia sxs from	ITT: 1. 323 2. 323 3. 325 PP: 1. 254 2. 235 3. 261 Attrition: 1. 20.4% 2. 26.3% 3. 18.7%	Primary Endpoint: Δ sSOL from baseline to 6 months: 1. -21.81 min 2. -28.21 min 3. -11.43 min LSGM Tx Ratio vs. PBO: 1. 0.732 (95% CI, 0.636 to 0.843; p<0.0001) 2. 0.701 (95% CI, 0.607 to 0.810; p<0.0001) Key Secondary Endpoints: Δ sSE from baseline to 6 months:	NA NA	Early Discontinuation from TEAE: 1. 4.1% 2. 8.3% 3. 3.8% TEAE: 1. 61.1% 2. 59.6% 3. 62.7% Severe TEAE: 1. 4.1% 2. 2.5% 3. 1.6%	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) randomization based on interactive computer-generated algorithm; stratified by age (≥64 y vs. younger) Performance Bias: (unclear) all personnel involved with the conduct and interpretation of the study, including investigators, site personnel and sponsor staff, were blinded to treatment allocation; however, method of blinding not described. Detection Bias: (high) data analyzed by mITT (participants were randomized and received ≥1 dose and had at least one post-dose primary efficacy measurement) with high early attrition in all arms.

	LEM dose, PBO randomized to 5 or 10 mg)	Sleep Diary which showed h/o sSOL ≥30 min or sWASO ≥60 min for ≥3 nights of past 7 nights -ISI score ≥15 -Reports 7-9 h spent in bed sleeping or trying to sleep -Reports habitual bedtime and waketime Key Exclusion Criteria: -Comorbid sleep disorder (sleep apnea, periodic limb movement disorder, RLS, circadian rhythm sleep disorder, narcolepsy) or h/o complex sleep-related behavior -Major medical or psychiatric disorder -Any person w/ a disorder inadequately treated -h/o abnormal nocturnal behaviors -Nocturia -Excessive caffeine consumption -h/o drug or alcohol dependency or abuse -Suvorexant treatment failure -Concurrent hypnotics or stimulants -Concurrent CYP3A inhibitor or inducer		1. LSM 14.19% 2. LSM 14.31% 3. LSM 9.64% LSM Tx Difference vs. PBO: 1. 4.55 (95% CI NR; p=0.0001) 2. 4.67 (95% CI NR; p<0.0001) Δ sWASO from baseline to 6 months: 1. LSM -46.75 min 2. LSM -41.95 min 3. LSM -29.28 min LSM Tx Difference vs. PBO: 1. -17.47 min (95% CI NR; p=0.0005) 2. -12.67 min (95% CI NR; p<0.0105) Δ sTST from baseline to 6 months: 1. LSM 69.95 min 2. LSM 74.08 min 3. LSM 51.40 min LSM Tx Difference vs. PBO: 1. 18.56 min (95% CI NR; p=0.0034) 2. 22.69 min (95% CI NR; p<0.0004)	 NA NA NA NA NA NA	Somnolence 1. 8.6% 2. 13.1% 3. 1.6% Headache: 1. 8.9% 2. 6.7% 3. 6.6% Arthralgia: 1. 4.5% 2. 1.0% 3. 2.8%		Attrition Bias: (high) attrition rate >20% for both LEM arms with higher than PBO. Reporting Bias: See NCT02783729 above. Other Bias: See NCT02783729 above. **Applicability**: Patient: strictly defined exclusion criteria including sleep disorders other than insomnia limited study enrollment at screening, limit real-life applicability. Intervention: New drug studied to establish efficacy and safety for FDA approval. Comparator: PBO used to establish efficacy. Outcomes: assessed sleep onset and sleep maintenance subjectively by diaries completed by each participant. Setting: 119 sites in North America (n=45), Europe (n=34), Asia (n=35), and Oceania (n=5).

Abbreviations: AHI = Apnea-Hypoapnea Index; ARR = absolute risk reduction; avg = average; BAI = Beck Anxiety Index; BDI-II = Beck Depression Inventory; BMI = body mass index; CBT = cognitive behavioral therapy; CI = confidence interval; CPAP = continuous positive airway pressure; DSM-5 = *Diagnostic and Statistical Manual of Mental Disorders* (5th Edition); ER = extended release; FDA = Food and Drug Administration; LEM = lemborexant; h = hours; h/o = history of; HepB = active viral hepatitis B; HepC = active viral hepatitis C; h/o = history of; hr = hours; ISI = Insomnia Severity Index; ITT = intention to treat; LPS = latency to persistent sleep; defined as minutes from lights off to the first epoch of 20 consecutive 30-second epochs of nonwakefulness); LSGM = least squares geometric mean; LSMD = least square mean difference; min = minutes; mITT = modified intention to treat; ms = milliseconds; MUPS = Munich Parasomnia Scale; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; OTC = over-the-counter; PBO = placebo; PLMI = Periodic Limb Movements Index; PP = per protocol; PSG = polysomnography; RLS = Restless Leg

Syndrome; SEA = serious adverse event; sSE = subjective sleep efficiency (the proportion of sTST per subjective time in bed); sSOL = subjective sleep onset latency (estimated time from attempt to sleep until sleep onset); sTST = subjective total sleep time (time spent asleep during their time in bed); sWASO = subjective wake-after-sleep onset (estimated sum of time of wake during the night after initial sleep onset until participant got out of bed for the day); sx = symptoms; TEAE = treatment emergent adverse event; tx = treatment; WASO = wake-after-sleep onset assessed by PSG; y = years; ZOL = zolpidem.
*Insomnia Criteria per DSM-5: 1) complains of dissatisfaction with nighttime sleep, in the form of difficulty staying asleep and/or awakening earlier in the morning than desired despite adequate opportunity for sleep; 2) frequency of complaint ≥3 times per week; 3) duration of complaint ≥3 months; and 4) associated with complaint of daytime impairment.

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
zolpidem tartrate	AMBIEN	TABLET	Y
zolpidem tartrate	ZOLPIDEM TARTRATE	TABLET	Y
diphenhydramine HCl	SLEEP AID	CAPSULE	N
diphenhydramine HCl	SLEEP TIME	CAPSULE	N
diphenhydramine HCl	Z-SLEEP	CAPSULE	N
diphenhydramine HCl	SLEEP AID	LIQUID	N
diphenhydramine HCl	SLEEP TIME	LIQUID	N
diphenhydramine HCl	Z-SLEEP	LIQUID	N
diphenhydramine HCl	NIGHTTIME SLEEP AID	TABLET	N
diphenhydramine HCl	SLEEP AID	TABLET	N
diphenhydramine HCl	SLEEP TABS	TABLET	N
doxepin HCl	DOXEPIN HCL	TABLET	N
doxepin HCl	SILENOR	TABLET	N
doxylamine succinate	SLEEP AID	TABLET	N
estazolam	ESTAZOLAM	TABLET	N
eszopiclone	ESZOPICLONE	TABLET	N
eszopiclone	LUNESTA	TABLET	N
flurazepam HCl	FLURAZEPAM HCL	CAPSULE	N
midazolam HCl	MIDAZOLAM HCL	SYRUP	N
ramelteon	RAMELTEON	TABLET	N
ramelteon	ROZEREM	TABLET	N
suvorexant	BELSOMRA	TABLET	N
tasimelteon	HETLIOZ	CAPSULE	N
temazepam	RESTORIL	CAPSULE	N
temazepam	TEMAZEPAM	CAPSULE	N
triazolam	HALCION	TABLET	N
triazolam	TRIAZOLAM	TABLET	N
zaleplon	ZALEPLON	CAPSULE	N
zolpidem tartrate	AMBIEN CR	TAB MPHASE	N
zolpidem tartrate	ZOLPIDEM TARTRATE ER	TAB MPHASE	N
zolpidem tartrate	EDLUAR	TAB SUBL	N
zolpidem tartrate	INTERMEZZO	TAB SUBL	N
zolpidem tartrate	ZOLPIDEM TARTRATE	TAB SUBL	N

Appendix 2: Abstracts of Comparative Clinical Trials

Hanna AH, Ramsingh D, Sullivan-Lewis W, et al. A comparison of midazolam and zolpidem as oral premedication in children, a prospective randomized double-blinded clinical trial.

Background: Anxiety associated with pediatric surgery can be stressful. Midazolam is a well-accepted anxiolytic in this setting. However, there are cases in which this medication is not effective. Zolpidem is a short-acting nonbenzodiazepine hypnotic drug that is administered orally and has quick onset of action (~15 minutes), and 2-3 hour duration.

Aims: Based on the theory that impaired perception following oral zolpidem administration would suppress the development of anxiety, we sought to compare zolpidem to midazolam for pediatric preoperative anxiety.

Methods: This prospective randomized double-blinded clinical trial was designed to compare the effectiveness of oral midazolam and zolpidem for anxiety premedication. Eighty ASA class I-II pediatric patients between 2 and 9 years old, surgery >2 hours, and at least 23 hours postoperative admission were included in the study. Randomization was done with 0.5 mg/kg midazolam or 0.25 mg/kg zolpidem administered orally. The primary outcome measure was between group difference in patient anxiety at the time of separation using the Modified Yale Preoperative Anxiety Scale. Secondary outcomes included emergence delirium and mask acceptance at induction.

Results: There was no significant difference in Modified Yale Preoperative Anxiety Scale scores at separation between midazolam (median/interquartile range = 26.7/ 23.3-36.6) and zolpidem (median/interquartile range = 30.0/23.3-56.6) groups, difference 0.01 (95% CI, $-3E^{-2}$ to $3E^{-2}$; p=0.07). Mask acceptance score was significantly better in the midazolam group. There was no significant difference in emergence delirium scores between groups.

Conclusion: This study demonstrates that zolpidem, as dosed, was similar to midazolam with regard to anxiety scoring, and inferior with regard to mask acceptance scores.

Impellizzeri P, Vinci E, Gugliandolo MC, et al. Premedication with melatonin vs midazolam: efficacy on anxiety and compliance in paediatric surgical patients.

Preoperative anxiety is a major problem in pediatric surgical patients. Melatonin has been used as a premedicant agent and data regarding effectiveness are controversial. The primary outcome of this randomized clinical trial was to evaluate the effectiveness of oral melatonin premedication, in comparison to midazolam, in reducing preoperative anxiety in children undergoing elective surgery. As secondary outcome, compliance to intravenous induction anesthesia was assessed. There were 80 children undergoing surgery randomly assigned, 40 per group, to receive oral midazolam (0.5 mg/kg, max 20 mg) or oral melatonin (0.5 mg/kg, max 20 mg). Trait anxiety of children and their mothers (State-Trait Anxiety Inventory) at admission, preoperative anxiety and during anesthesia induction (Modified Yale Pre-operative Anxiety Scale), and children's compliance with anesthesia induction (Induction Compliance Checklist) were all assessed. Children premedicated with melatonin and midazolam did not show significant differences in preoperative anxiety levels, either in the preoperative room or during anesthesia induction. Moreover, compliance during anesthesia induction was similar in both groups. Conclusions: This study adds new encouraging data, further supporting the potential use of melatonin premedication in reducing anxiety and improving compliance to induction of anesthesia in children undergoing surgery. Nevertheless, further larger controlled clinical trials are needed to confirm the real effectiveness of melatonin as a premedicant agent in pediatric population.

Yu ZH, Xu XH, Wang SD, et al. Effect and safety of paroxetine combined with zolpidem in treatment of primary insomnia.

Purpose: Primary insomnia is a persistent and recurrent disorder as well as a risk factor for depression. The aim of this study was to determine whether the zolpidem combined with paroxetine would be effective in the treatment of patients with primary insomnia.

Methods: Ninety patients meeting DSM-IV criteria for primary insomnia were randomly assigned to 8 weeks of treatment with zolpidem combined with paroxetine (the combined treatment group, n = 45) or zolpidem combined with placebo (the control group, n = 45). Patients were assessed with the Pittsburgh

Sleep Quality Index (PSQI), polysomnography (PSG), and the Treatment Emergent Symptom Scale (TESS). Results Compared with the control group, the combined treatment group was more significantly improved on wake time after sleep onset (WASO), total sleep time (TST), sleep efficiency (SE), and total PSQI scores, but not the sleep onset latency (SOL).
Conclusions: Eight weeks of the zolpidem combined with paroxetine treatment to patients with primary insomnia is more effective than zolpidem treatment only in sleep maintenance and early morning awakenings.

Appendix 3: Medline Search Strategy

Ovid MEDLINE, ALL: 1946 to April 23, 2020
1 exp Zolpidem/ 1589
2 exp Diphenhydramine/ 4382
3 exp Doxepin/ 822
4 exp Doxylamine/ 381
5 exp Estazolam/ 105
6 exp Eszopiclone/ 116
7 exp Flurazepam/ 780
8 exp Midazolam/ 8770
9 ramelteon.mp. 395
10 suvorexant.mp. 235
11 tasimelteon.mp. 75
12 exp Temazepam/ 668
13 exp Triazolam/ 1233
14 zaleplon.mp. 398
15 exp "Sleep Initiation and Maintenance Disorders"/ 13026
16 exp "Hypnotics and Sedatives"/ 122457
17 exp Sleep Wake Disorders/ 88013
18 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 19149
19 15 or 16 or 17 206256
20 limit 19 to (english language and yr="2017 -Current" and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial 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")) 3063
21 18 and 19 and 20 290

Appendix 4: Prescribing Information Highlights

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

DAYVIGO™ (lemborexant) tablets, for oral use, [controlled substance schedule pending]
Initial U.S. Approval: [pending controlled substance scheduling]

----------INDICATIONS AND USAGE----------
DAYVIGO is an orexin receptor antagonist indicated for the treatment of adult patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance. (1)

----------DOSAGE AND ADMINISTRATION----------
- Recommended dose is 5 mg taken no more than once per night, immediately before going to bed, with at least 7 hours remaining before the planned time of awakening. Dosage may be increased to 10 mg based on clinical response and tolerability. (2.1)
- The maximum recommended dose is 10 mg once daily. (2.1)
- Time to sleep onset may be delayed if taken with or soon after a meal. (2.1)
- Hepatic Impairment: (2.3)
  - Moderate hepatic impairment: Initial and maximum recommended dosage is 5 mg no more than once per night.
  - Severe hepatic impairment: Not recommended.

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 5 mg, 10 mg (3)

----------CONTRAINDICATIONS----------
DAYVIGO is contraindicated in patients with narcolepsy. (4)

----------WARNINGS AND PRECAUTIONS----------
- CNS Depressant Effects and Daytime Impairment: Impairs alertness and motor coordination including morning impairment. Risk increases with dose and use with other central nervous system (CNS) depressants. For patients taking DAYVIGO 10 mg, caution against next-day driving and other activities requiring complete mental alertness. (5.1)
- Sleep Paralysis, Hypnogogic/Hypnopompic Hallucinations, and Cataplexy-like Symptoms: May occur with use of DAYVIGO. (5.2)
- Complex Sleep Behaviors: Behaviors including sleep-walking, sleep-driving, and engaging in other activities while not fully awake may occur. Discontinue immediately if a complex sleep behavior occurs. (5.3)
- Compromised Respiratory Function: Effect on respiratory function should be considered. (5.4, 8.8)
- Worsening of Depression/Suicidal Ideation: Worsening of depression or suicidal thinking may occur. Prescribe the lowest number of tablets feasible to avoid intentional overdosage. (5.5)
- Need to Evaluate for Co-morbid Diagnoses: Reevaluate if insomnia persists after 7 to 10 days of treatment. (5.6)

----------ADVERSE REACTIONS----------
The most common adverse reaction (reported in ≥5% of patients treated with DAYVIGO and at least twice the rate of placebo) was somnolence. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eisai Inc. at 1-888-274-2378 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Strong or moderate CYP3A inhibitors: Avoid concomitant use. (7.1)
- Weak CYP3A inhibitors: The maximum recommended dose is 5 mg. (2.2, 7.1)
- Strong or moderate CYP3A inducers: Avoid concomitant use. (7.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2019

Appendix 5: Key Inclusion Criteria

Population	Patients diagnosed with primary chronic insomnia
Intervention	Diphenhydramine Doxepin Doxylamine Estazolam Eszopiclone Flurazepam Midazolam Ramelteon Suvorexant Tasimelteon Temazepam Triazolam Zaleplon Zolpidem [melatonin, tiagabine, trazodone]
Comparator	Active Intervention Above Placebo
Outcomes	Sleep latency (SL) Total sleep time (TST) Wake after sleep onset (WASO) Quality of sleep (QOS) Sleep efficiency (SE) Number of awakenings (NOA)
Timing	At least 4 weeks
Setting	Outpatient

Sedatives

Goal(s):

- Restrict use of sedatives to OHP-funded conditions. Treatment of uncomplicated insomnia is not funded; insomnia contributing to covered co-morbid conditions is funded.
- Prevent concomitant use of sedatives, including concomitant use with benzodiazepines or~~, and~~ opioids.
- ~~Restrict long-term sedative use to due to insufficient evidence and to limit adverse effects.~~
- Limit daily zolpidem dose to~~use~~ the maximum ~~FDA~~ recommended daily dose by the FDA~~based on gender~~.

Length of Authorization:

Up to 12 months or lifetime (criteria-specific)

Requires PA:

- All sedatives except melatonin
- ~~Concomitant use of more than one benzodiazepine, more than one non-benzodiazepine sedative, or the combination of a benzodiazepine and non-benzodiazepine sedative in the prior 30 days~~
- ~~Sedatives that exceed a total quantity of 30 doses within 60 days~~

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/

Zolpidem Daily Quantity Limits

Generic	Brand	Max Daily Dose ~~Male~~ ~~Female~~
Zolpidem ~~IR~~	Ambien	10 mg ~~(initial and maximum dose)~~ ~~5 mg (initial maximum dose)~~ ~~10 mg (maximum dose)~~
Zolpidem ER	Ambien CR	12.5 mg ~~(initial and maximum dose)~~ ~~6.25 mg (initial maximum dose)~~ ~~12.5 mg (maximum dose)~~

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for zolpidem at a higher dose than listed in the quantity limit chart?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #3
3. Is the request for a non-preferred product and will the prescriber consider a change to a preferred product? Message: Preferred products are evidence-based and reviewed for comparative effectiveness and safety by the P&T Committee.	**Yes:** Inform prescriber of preferred alternatives in class.	**No:** Go to #4
4. Is the patient being treated under palliative care services (ICD10 Z51.5) with a life-threatening illness or severe advanced illness expected to progress toward dying?	**Yes:** Approve for lifetime.	**No:** Go to #5
5. Has the patient been treated with another non-benzodiazepine sedative, benzodiazepine, or opioid within the past 30 days?	**Yes:** Go to #6	**No:** ~~Pass to RPh;~~ Go to #7
6. Is this a switch in sedative therapy due to intolerance, allergy or ineffectiveness?	**Yes:** Document reason for switch and approve duplication for 30 days.	**No:** Pass to RPh. Deny; medical appropriateness.
~~5.~~7. Does the patient have a diagnosis of insomnia with obstructive sleep apnea?	**Yes:** Go to #~~8~~6	**No:** Go to #~~9~~7
~~6.~~8. Is patient on CPAP?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh. Deny; medical appropriateness. Sedative/hypnotics are contraindicated~~,~~ due to depressant effect~~, are contraindicated~~.

Approval Criteria		
~~7.~~9. Is the patient being treated for co-morbid: • Depression; • Anxiety or panic disorder; or • Bipolar disorder? **AND** Is there an existing claim history for treatment of the co-morbid condition (e.g., antidepressant, lithium, lamotrigine, antipsychotic, or other appropriate mental health drug)?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh; Go to #10~~8~~
~~8. Has the patient been treated with another non-benzodiazepine sedative, benzodiazepine, or opioid within the past 30 days?~~	~~**Yes:** Go to #9~~	~~**No:** Pass to RPh; Go to #10~~
~~12. Is this a switch in sedative therapy due to intolerance, allergy or ineffectiveness?~~	~~**Yes:** Document reason for switch and approve duplication for 30 days.~~	~~**No:** Pass to RPh. Deny; medical appropriateness.~~
~~16.~~10. RPh only: Is diagnosis being treated a funded condition and is there medical evidence of benefit for the prescribed sedative?	**Funded:** Document supporting literature and approve up to 6 months with subsequent approvals dependent on follow-up and documented response.	**Not Funded:** Go to #11
~~17.~~11. RPh only: Is this a request for continuation therapy for a patient with a history of chronic benzodiazepine use where discontinuation would be difficult or unadvisable?	**Yes:** Document length of treatment and last follow-up date. Approve for up to 12 months.	**No:** Deny; medical appropriateness

P&T/DUR Review: *12/20 (AG);* *7/18 (JP); 3/17; 11/20/14, 3/27/14, 5/18/06, 2/23/06, 11/10/05, 9/15/05, 2/24/04, 2/5/02, 9/7/01*
Implementation: *TBD;* *8/15/18; 1/1/15, 7/1/14; 1/1/07, 7/1/06, 11/15/05*

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

New Drug Evaluation: Teprotumumab, 500mg, intravenous injection

Date of Review: December 2020
End Date of Literature Search: 07/28/2020
Generic Name: Teprotumumab-trbw
Brand Name (Manufacturer): Tepezza® (Horizon Therapeutics, Inc.)

Dossier Received: yes

Research Questions:

1. What is the efficacy of teprotumumab for the treatment of thyroid eye disease?
2. Is there comparative evidence for treatments of thyroid eye disease?
3. Is teprotumumab safe for the treatment of thyroid eye disease?
4. Is there comparative evidence for the safety of drug therapy in patients being treated for thyroid eye disease?
5. Are there sub-populations (based on age, gender, ethnicity, comorbidities, disease duration, or severity) of patients with thyroid eye disease for which teprotumumab is more effective or associated with fewer adverse events?

Conclusions:

- A 2017 phase 2, randomized, double-blind, placebo controlled study assessed the efficacy and safety of teprotumumab versus placebo in the treatment of active thyroid eye disease (TED) associated with Graves' disease (GD).[1] (poor quality)
    - Limitations include a surrogate endpoint for vision loss or surgical need, use of clinical activity score (CAS) as component of primary endpoint, unknown duration of response, lack of targeted applicability based on disease severity, and potentially high selection, detection, reporting, and "other" bias.
- A 2020 phase 3, randomized, double-blind, placebo controlled study assessed the efficacy and safety of teprotumumab versus placebo in the treatment of active, moderate to severe TED associated with GD.[2] (poor quality)
    - Limitations include a surrogate endpoint for vision loss or surgical need, unknown duration of response, and potentially high detection, reporting, and "other" bias.
- There is moderate quality evidence that teprotumumab showed a greater response rate compared to placebo using a composite endpoint of proptosis reduction of at least 2 mm and CAS reduction of at least 2 points over a period of 24 weeks {[69% vs. 20%; odds ratio (OR) 8.86, 95% confidence interval (CI) 3.29 to 23.8; P<0.001); absolute risk reduction (ARR) 49%, number needed to treat (NNT) 3][1][78% vs 7%; difference 72.46%, 95% CI 57.57% to 87.35%; P<0.001; ARR 71%, NNT 2][2]}.
- There is moderate quality evidence that teprotumumab showed a reduction of proptosis of at least 2 mm compared to placebo over a period of 24 weeks [(Change from baseline -2.46±0.2mm vs -0.15±0.19mm, P<0.001)[1](83% vs. 10%; difference 73%, 95% CI 59% to 88%, p<0.001; ARR 73%, NNT 2)[2]]
- There is insufficient evidence for safety as fewer than 100 total patients have received this medication. Most common adverse events were muscle spasms (25%), nausea (17%), and alopecia (13%).[1-3] Infusion reaction resulted in study discontinuation for one patient.[2]
- There is insufficient evidence regarding duration of response beyond 24 weeks or for clinical outcomes of vision loss or surgical need.[1,2]

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- There is no evidence regarding place in therapy in relation to current standard of care (pulse corticosteroids) or in patients with sight-threatening disease.[1,2]
- There is high potential for teratogenicity with fetal exposure to this medication.[3]

Recommendations:

- Designate teprotumumab-trbw as non-preferred on the Oregon Health Plan (OHP) Practitioner-Managed Prescription Drug Plan
- Implement clinical prior authorization for teprotumumab-trbw to ensure appropriate utilization. **(Appendix 2)**
- Evaluate costs in executive session.

Background:

Hyperthyroidism, caused by an inappropriately high synthesis and secretion of thyroid hormones, is a relatively common condition in the United States (US).[4] Overt hyperthyroidism affects an estimated 0.5% of adults, while subclinical hyperthyroidism has a prevalence of 0.7%.[4] Graves' disease is the most common cause of hyperthyroidism and accounts for 50-80% of the cases.[5] The female to male prevalence of GD is 5:1.[5]

Thyroid eye disease is an inflammatory eye disease of the orbit that develops in conjunction with autoimmune thyroid disorders. It is also known in the medical literature as dysthyroid eye disease, thyroid orbitopathy, thyroid-associated ophthalmopathy, and thyroid-associated orbitopathy. When associated specifically with GD, additional names include Graves' eye disease, Graves' orbitopathy, Graves' ophthalmopathy, and Graves' dysthyroid opthalmopathy.[6,7] TED is the result of inflammation in both the orbital connective tissue and extraocular muscles, with eventual fibrosis of the extraocular muscles and adipogenesis within the orbits.[8] Patient symptoms may include sore, gritty, or red eyes, double vision, reduction of vision, and loss of vision.[9] Clinical signs include periorbital edema, lid lag, lid retraction, chemosis, exophthalmos, and dysmotility. More severe forms may result in exposure keratopathy, diplopia, and compressive optic neuropathy. Vision loss can occur about 3-7% of those with TED due to corneal exposure (exposure keratopathy) or compressive optic neuropathy (dysthyroid optic neuropathy).[9,10] Mild cases may still result in significant quality of life (QoL) reductions in affected patients.[8,9] TED generally follows a biphasic course and is usually self-limiting.[11,12] There is an 18-36 month active phase with ongoing inflammation accompanied by rapid deterioration, followed by a stable or inactive phase that often results in regression of many signs and symptoms toward baseline, though vision loss may be permanent.[4,11,12] A group of 59 patients with TED who had never received medical or surgical treatment for eye disease at presentation to a specialty thyroid-eye clinic were then followed for a median of 12 months to study the natural disease course; 22.0% improved substantially, 42.4% showed minor improvement, 22% were unchanged, and 13.5% continued to deteriorate necessitating immunosuppressant treatment.[13]

Roughly 90% of TED cases are in patients with current or a history of GD. Other thyroid disorders, such as Hashimoto's thyroiditis, an autoimmune condition generally resulting in hypothyroidism, also have been associated with TED. Severity is usually classified as sight-threatening, moderate to severe, and mild.[11] Symptomatic TED develops in roughly 30-50% of patients with GD,[4,8,9] though magnetic resonance imaging (MRI) or computed topography (CT) have shown extraocular muscle enlargement in as many as 70% of patients.[8] Only 5% of patients with GD go on to develop moderate or severe TED.[4] Smoking increases risk of developing TED by 7 to 8 fold,[10] as well as the severity of TED, particularly after radioactive iodine (RAI) therapy for hyperthyroidism.[11] There is a demonstrated dose-response relationship to number of cigarettes/day and likelihood of TED development. Continued smoking may hinder the effectiveness of historical treatments such as corticosteroids, though data are lacking for if this remains true with newer therapies.[4,11] Women are more likely to develop GD and men may be at higher risk of developing severe TED. However, the sex-related risk is unclear and may be associated with historical population tobacco-use patterns.[4] More severe cases of TED are generally seen in elderly patients.[4] Incidence peaks during the 5th and 6th decades of life with a median age at diagnosis of 43 years.[4,10] Incidence rates of 16/100,000 in women and 2.9/100,000 in men, with an overall calculated prevalence of 0.25% have been reported.[9] Additional risk factors included for TED development in the setting of GD are RAI use for definitive treatment of hyperthyroidism, untreated hyperthyroidism, and post-

treatment hypothyroidism.[4] Most patients with active TED at time of RAI receive prophylactic oral corticosteroids (CS) beginning 1-3 days post-RAI dosed at 0.4-0.5 mg/kg/day prednisone equivalent for one month, then tapered over 2 months, to prevent TED progression.[4] Thyroid-stimulating hormone receptor autoantibodies are also an independent risk factor for severity and progression of TED.[12] A family history of TED is present in 61% of TED patients.[10] In patients who receive surgical treatment for GD, total thyroidectomy is more effective at preventing recurrent hyperthyroidism than subtotal thyroidectomy (including both bilateral subtotal thyroidectomy and the Dunhill procedure). However, surgery type does not affect regression of TED.[5] Antithyroid medications (e.g. methimazole, propylthiouracil) may be used to manage hyperthyroidism without affecting the disease course of TED.[11]

Sight-threatening disease with dysthyroid optic neuropathy should be treated with intravenous (IV) CS, followed by surgical decompression if there are CS contraindications or no response to IV CS therapy after 1-2 weeks.[11] Moderate to severe disease is currently managed with IV CS with or without orbital radiotherapy (OR).[6,11] Orbital inflammation is reduced by IV CS in 50-80% of treated patients with moderate-severe TED, though there is an estimated 11% relapse rate at 12 weeks.[14] Sight-threatening corneal breakdown is addressed with aggressive topical lubrication and consideration for CS or surgery when lubricants are ineffective. Patients with moderate to severe active TED should receive IV CS pulses, with consideration for OR in patients with diplopia or restricted motility who lack contraindications (e.g. diabetic retinopathy, severe hypertension).[11] Oral steroids generally have a total daily dose of 80-100 mg prednisone (~1 mg/kg) and are tapered over 2-3 months.[11] IV CS have multiple studied dosing regimens including 15 mg/kg infusions for 4 cycles with each cycle being two infusions on alternate days at 2 week intervals, followed by 7.5 mg/kg for an additional 4 cycles for a total dose of 9-12 grams; this regimen was used following RAI.[15] Alternatively, 500 mg IV methylprednisolone daily for 3 days each week for 4 weeks has also been used.[16] The use of IV CS is considered more effective than oral CS based on two studies which show response rates of 77-88% for IV CS (± radiotherapy) compared to 51-63% for oral CS (± radiotherapy).[11] Disease can flare when tapering or discontinuing steroids.[11] The use of CS in mild TED is rarely appropriate.[11] Other therapies have been studied in TED, but none have high-quality data supporting their use.[9,14] A 2018 Cochrane review of tocilizumab in TED found no studies that met their inclusion criteria.[9] An older Cochrane review on rituximab also found no acceptable studies, but three more recent publications have shown mixed results.[8,17-19] These prospective, randomized studies include: no difference versus placebo, statistical improvement from baseline with rituximab + RAI similar to the improvement of CS + RAI, and statistical superiority of rituximab at week 24 compared CS.[17-19] Additional immunosupressants that have been studied in the literature include mycophenolate mofetil, azathioprine, cyclosporine, and methotrexate.[14] Additional therapies which have been studied include somatostatin analogs, botulinum toxin (for upper lid retraction), and selenium supplementation.[4,11] None of these medications hold Food and Drug Administration (FDA) approvals for usage in TED and the data for their use remains mixed, though rituximab, tocilizumab, and mycophenolate mofetil have shown the most potential.[14]

There are several scales and classification systems used to describe thyroid eye disease as the understanding of this disease has developed over time. The disease is characterized by both *severity* and if it is *active* or *inactive*. The NO SPECS Classification (also called Werner's classification system) was first introduced in 1969 and modified in 1977 and refers to no physical signs or symptoms, only signs, soft tissue involvement, proptosis, extraocular involvement, corneal involvement, and sight loss due to optic nerve involvement; though it is less utilized than other classification modalities currently available today it was used in many older studies to evaluate efficacy.[9] This classification system grades clinical severity, but does not differentiate between inflammatory progressive and non-inflammatory status.

The American Thyroid Association (ATA) recommends the severity assessment seen in **Table 1** for Graves' orbitpathy.[4,9] The European Group of Graves' Orbitopathy (EUGOGO) defines severity similarly, though moderate to severe is a combined category of severity **(Table 2)**.[11]

The Clinical Activity Score (CAS) is commonly used and it differentiates active from non-active forms of TED (**Table 3**). The 10-point (10 item) version requires 2 clinical examinations as 3 items reflect change in clinical signs. A score of 3 of 7 at first examination or 4 of 10 after repeat examination indicates active disease,

though a score of at least 4 of 7 has been required in some medication trials.[9] The EUGOGO modified this scoring to only use the 7 items that do not require repeat examination, and exclude change in visual acuity, diplopia, or proptosis.[9] CAS was originally validated based on its ability to correctly predict response to 12 weeks of tapered oral prednisone or OR treatment, in 43 patients with moderate to severe Graves' ophthalmopathy.[20] These patients were 20-75 years old and had been euthyroid for at least 3 months.[20] This validation study determined that a CAS at least 4 of 7 on the initial assessment had a sensitivity of 55% and specificity of 86%. With an assumed 35% non-response rate, this led to a positive predictive value of 80% and negative predictive value of 64% of a change of at least one NO SPECS class.[20] It is important to note that increased sympathetic state caused by hyperthyroidism can result in lid retraction or stare. When these are present without associated eye changes they are not thought to be part of TED and should be scored as absent on CAS.[4]

An additional classification known as the VISA Classification (vision, inflammation, strabismus, and appearance/exposure) is used to assess both severity and activity, and is often used in the United States (US), though less often in Europe.[9,12] Each of the 4 inputs has multiple severity parameters and it is graded independently, with a maximum possible score of 20.[12] The inflammatory input component of VISA has a maximum score of 10, with 4 or less considered moderate and 5 or above considered severe.[12] The EUGOGO Classification uses the CAS as to evaluate activity, while severity are compared to an image atlas developed by the group.[11,12]

EUGOGO has specific severity measures recommended during patient assessment.[11,21] The Clinical Measures of Severity Score (CSS) is based on these severity measures. Each CSS item should be considered an individual parameter, as there is no overall score and use of this tool in literature was just introduced in studies evaluated below.[11,21,22]

EUGOGO has developed several QoL tools including Graves' orbitopathy (GO) quality of life questionnaire (GO-QOL), GO quality of life scale (GO-QLS), and TED quality of life questionnaire (TED-QOL).[12] These have shown moderate correlation to disease severity.[12] The GO-QOL includes a visual functioning subscale (score 0-100) and an appearance subscale (score 0-100), these can be assessed independently or in combination (overall score range 0-100).

EUGOGO has made recommendations for minimum changes to objective parameters for assessing response in clinical trials.[21] These include a CAS change of ≥ 2, proptosis change of ≥ 2 mm, and subjective diplopia change of at least 1 grade. For subjective parameters, the GO-QOL is considered valid and a ≥ 6 point change on either subscale is considered meaningful, though an overall minimum score change was not explicitly defined.[21] The FDA considers a 2 mm reduction in proptosis clinically meaningful as it is expected to reduce diplopia and improve corneal lid coverage.[10] The FDA has not been provided with validation information on the GO-QOL and therefore does not currently include results interpretation in drug reviews.[10] Furthermore, changes in CAS are not accepted by the FDA as an appropriate measurement of response as "there is not necessarily equal weight for each component".[10]

Table 1: Graves' Orbitopathy Severity Assessment[4]

Grade	Lid retraction	Soft tissues	Proptosis*	Diplopia	Corneal exposure	Optic nerve status
Mild	< 2 mm	Mild involvement	< 3 mm	Transient or absent	Absent	Normal
Moderate	2 mm	Moderate involvement	3 mm	Inconstant	Mild	Normal
Severe	2 mm	Severe involvement	3 mm	Constant	Mild	Normal
Sight threatening	-	-	-	-	Severe	Compression

Abbreviations: F/M = female/male; mm = millimeter

* Variation compared to upper limit of normal for race/sex or the patient's baseline (if available)

Table 2: EUGOGO Disease Severity for Graves' Orbitopathy[21]

Severity	Specific signs/symptoms	General Management
Mild	Typically one or more of following: minor lid retraction ≤2mm, mild soft tissue involvement, exophthalmos < 3mm above normal for race and gender, transient or no diplopia, corneal exposure responsive to lubricants.	• Minor impact on daily life • Disease not sufficient to justify immunosuppressive or surgical treatment
Moderate to Severe	Typically one or more of following: Lid retraction ≥ 2mm, moderate-severe soft tissue involvement, exophthalmos ≥3mm above normal for race and gender, inconstant or constant diplopia	• Not sight threatening • Disease has sufficient impact on daily life to justify immunosuppression (active disease) or surgical intervention (inactive disease)
Sight threatening	Dysthyroid optic neuropathy and/or corneal breakdown	• Immediate intervention needed

Table 3: Clinical Activity Score[4,12]

Elements	**Each visit**	**Comparison with previous visit**	**Score**
Painful feeling behind the globe over last 4 weeks	X		1
Pain with eye movement during last 4 weeks	X		1
Redness of the eyelids	X		1
Redness of the conjunctiva	X		1
Swelling of the eyelids	X		1
Chemosis (edema of the conjunctiva)	X		1
Swollen caruncle (flesh body at medial angle of the eye) *and/or plica**	X		1
Increase in proptosis greater than or equal to 2 mm		X	1
Decreased eye movements greater than or equal to 5° *(or greater than or equal to 8°)** in any direction		X	1
Decreased visual acuity greater than or equal to 1 line on Snellen chart		X	1

* Modifications for EUGOGO CAS in italics

Teprotumumab was approved in January 2020 as an orphan drug for the treatment of thyroid eye disease.[3]

As of October 2020, there has not been any previous usage of teprotumumab in the OHP fee-for-service (FFS) population. It is estimated that fewer than 20 patients are currently receiving corticosteroids or off-label immunosuppressant therapies for TED. Approximately 450 FFS OHP patients have had claims related to Graves' disease in 4th quarter 2019 through 1st quarter 2020, leading to an estimated 23 patients with moderate-severe TED using a 5% historical incidence rate. Given that the risk of severe TED increases with age and that not all patients may be in the active phase of disease, this may be an overestimation in the Medicaid population.

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

Clinical Efficacy:
Teprotumumab is a first in class insulin-like growth factor-1 receptor inhibitor (IGF-1R). It is approved for use in TED, though details of its mechanism of improvement are not fully characterized.[3]

The efficacy and safety of teprotumumab was evaluated in a phase 2, randomized, placebo-controlled, double-masked trial (NCT01868997).[1,10,22,23] Participants were randomized using an interactive web response system and stratified by smoking status at each site to receive teprotumumab infusions (n=42) of 10 mg/kg initially, followed by 20 mg/kg or matching placebo infusions (n=45) every 3 weeks for 24 weeks, then a 48 week follow up period (n=39 post-teprotumumab, n=36 post-placebo).[1,22] Patients had a history of GD and active TED, defined as a CAS of at least 4, and ophthalmic symptoms for no more than 9 months prior to enrollment.[1,22] Patients were initially included if euthyroid and stable on at least 2 months of antithyroid medication or with a history of RAI or surgical thyroidectomy.[22] This was amended early in recruitment to euthyroid with excursions of free triiodothyronine (T3) and free thyroxine (T4) allowed to no more than 50% above or below normal levels; there was no specific requirement for underlying treatment of GD.[22] Previous medical or surgical treatment for TED was not allowed, except up to 1 gram of oral methylprednisolone equivalent with a 6 week washout.[1,22] See Table 6 for additional inclusion and exclusion criteria.

The study began in July 2013 and had a primary completion date of March 2016.[24] The primary and secondary endpoints, assessed at week 24, were amended in Sept 2015.[22] The authors report that there was no interim data analysis.[1] The primary endpoint assessed difference in rate of response to treatment and initially defined a "responder" as a patient with a CAS decrease of ≥ 2 points or improvement in ductions of ≥ 10 degrees or a reduction of proptosis of ≥ 2mm with no deterioration in non-study eye.[22] This was altered to a composite endpoint where a responder required both CAS and proptosis improvements while having no deterioration of the non-study eye.[22] Mobility restriction was removed as a measure in the primary and secondary endpoints. Final secondary endpoints were reported as GO-QOL, proptosis, and CAS.[22] Mobility restriction, time to response, and CSS were changed to exploratory endpoints.[1,22,23]

Participants had an average age of 52.9 years and were primarily female (73.6%) and White (86.2%). The teprotumumab group had a statistically significantly higher response rate when compared to placebo at week 24 [69% vs. 20%; odds ratio (OR) 8.86, 95% confidence interval (CI) 3.29 to 23.8; P<0.001)] in the intention to treat (ITT) population.[1] Change in proptosis from baseline for teprotumumab (-2.46±0.20mm) versus placebo (-0.15±0.19mm) was also statistically significant (P<0.001), as was change in CAS for teprotumumab (-3.43±0.18) versus placebo (-1.85±0.17; P<0.001).[1] The QOL assessments found statistically significant difference Overall (teprotumumab 17.7±2.4 vs. placebo 6.8±2.3; P<0.01) and in the Visual-functioning subscale (teprotumumab 21.7±2.9 vs. placebo 7.5±2.7; P<0.001), but not the Appearance subscale (teprotumumab 12.9±2.8 vs. placebo 6.6±2.7; P=0.10).[1]

This study met the primary endpoint, however, until publication of data of the follow-up period of this study, the duration of response is unknown. There is concern for relapse given the active period of up to 36 months during the disease course of TED (see "other relevant outcomes" from follow-up period, **Table 6**).[10] Longer term data may also elucidate if this therapy is effective for the clinical goal of reduction of vision loss due to TED. There is possible selection bias between groups. Despite stratification, only 26% of teprotumumab patients compared to 41% of placebo patients were smokers; the authors had anticipated approximately 50% of participants would be smokers.[1,22] There was also imbalance in the free T3 and free T4 levels between groups. More teprotumumab (46%) versus placebo (30%) patients were euthyroid at baseline, and this continued when comparing values occasionally out of normal range (teprotumumab 42% vs. placebo 57%), though groups were similar for values sustained out of range (teprotumumab 12% vs. placebo 14%).[1,23] Untreated hyperthyroidism and post-

treatment hypothyroidism are TED risk factors.[4] Additionally, sympathetic activation from hyperthyroidism can result in eye changes such as lid retraction and stare, which can hinder accurate CAS scoring.[4] There is concern whether previous thyroid treatment was accurately recorded as 62% of teprotumumab patients and 59% of placebo patients were receiving levothyroxine or thyroid extract at baseline[1] while only 22.7% and 23.2% from each group were reported to have had previous RAI or surgical thyroidectomy.[23] Also, three patients received the wrong treatment.[10] It is unclear if the amended endpoints introduce reporting bias as the updated primary endpoint appears more stringent. Ophthalmic assessments were performed by the same clinician throughout the study period with each patient when possible. Although this method may have increased efficiency and consistency, this continuity could possibly have led to unblinding for patients in the treatment group with a notable early proptosis response and detection bias in subjective variables such as components of the CAS. Detection bias may explain the large difference in responder rates between groups and overall low placebo responder rate, particularly given that TED is often self-limiting and has been shown to improve to some extent in more than 50% of patients without treatment over a 12 month period.[13] Targeted applicability is limited by omission of severity rating from inclusion criteria[1,10,22] as TED should be categorized by activity and severity.[4] This omission also complicates placement in therapy; current therapies of pulse steroids, surgery, and OR are used in relation to severity during active disease. Baseline reporting of severity would have been appropriate for group comparison as well. There is additional potential bias due to industry involvement in trial design, funding, and oversight. Overall this trial is judge to be of poor quality due to risk of bias.

Teprotumumab was evaluated in a second study, a phase 3, randomized, placebo-controlled, double-masked trial (NCT03298867).[2,10,25,26] The randomization process and drug intervention were the same as the previously described study.[2,25] Inclusion and exclusion criteria were similar, though with the important addition that patients were required to have moderate to severe TED as defined by parameters consistent with the Graves' Orbitopathy Severity Assessment.[2,25] There were 41 patients in the teprotumumab group and 42 who were randomized to receive placebo. Patients had an average age of 50.2 years and were primarily female (72.3 %) and White (86.7%).

A proptosis reduction of ≥ 2mm at week 24 was the primary endpoint and 83% of teprotumumab patients and 10% of placebo patients achieved this response (difference 73%, 95% CI 59% to 88%, p<0.001).[2] Teprotumumab was statistically superior to placebo in all secondary endpoints as well **(Table 6)**, including combined proptosis response and CAS reduction of ≥ 2 points at week 24 (teprotumumab 78% vs. placebo 7%, difference 71%, 95% CI 56% to 86%, p<0.001).[2] Diplopia was added as a secondary endpoint via amendment on Jan 31st, 2019, just prior to the primary study completion date of Feb 13th, 2019.[25,27]

The baseline patient characteristics of the groups in this study were well balanced including smoking status, though previous history of thyroid treatment (specifically RAI) was not reported and thyroid hormone levels were only presented as mean and median values with ranges. Quality of thyroid control as described by time within range between the groups was unable to be evaluated. The reported duration of GD was very different in the two studies, with a mean of 10.7-10.8 months in the Smith et al study, but a mean of 2.2-3.5 years in the Douglas et al study, though it is unclear if this has any clinical significance.[1,2] This study also used the same clinician to perform the ophthalmic evaluations and is subject to the same potential detection bias. The extreme differences in the treatment and placebo group are again notable, with only 7% placebo response to the composite secondary endpoint (compared with 20% placebo response in the initial study), despite the natural disease course of TED and less than half of the smoking rate compared to the placebo group in the initial study. Data from the follow-up period regarding duration of effect are not currently available. There is potential for reporting bias due to the amended secondary endpoint, and other bias from industry involvement as well. This trial is also judged to be of poor quality due to risk of bias.

In summary, teprotumumab is a newly approved agent for TED which has shown moderate quality of evidence for reduction of proptosis of at least 2 mm and for a composite endpoint of response using proptosis reduction of at least 2 mm and CAS reduction of at least 2 points when compared to placebo in patients with active, moderate to severe TED after 24 weeks. Evidence was demoted due to multiple methodologic sources of potential bias creating an overall high risk

of bias **(Table 6)** and promoted due to large magnitude of effect with consistency between studies. The FDA does not recognize the CAS scale as an appropriate primary endpoint measure.[10] There is insufficient evidence regarding duration of response beyond 24 weeks, clinical outcomes of vision loss and surgical need, and for safety. There is no evidence regarding place in therapy in relation to current standard of care (pulse corticosteroids) or in patients with sight-threatening disease.

Clinical Safety:
Labeled clinical warnings for teprotumumab include infusion reactions, exacerbation of irritable bowel disease (IBD), and hyperglycemia. Most adverse effects (AE) in the studies were mild in severity. AEs are found in **Table 4**. Infusion reactions, generally mild or moderate, may occur at any time during and up to 1.5 hours after any infusion. One patient discontinued treatment after infusion reaction.[2] After a reaction, subsequent infusions can include premedicaton with an antihistamine, antipyretic, CS, and/or a slower medication infusion rate.[3] Patients with preexisting IBD should be monitored for flare. Clinicians should consider teprotumumab discontinuation if an IBD exacerbation occurs. Hyperglycemia was seen in 10% of teprotumumab treated patients, with two-thirds of these patients reporting preexisting diabetes.[3] Blood glucose should be monitored throughout treatment and patients with preexisting diabetes should be controlled prior to initiation of teprotumumab.[3] Modification of medications may be needed during treatment to regain glycemic control in diabetic patients.[1]

Teprotumumab is highly suspected to result in fetal harm due to evidence from animal based studies and its mechanistic inhibition of IGF-1R.[3] Exposure in pregnant monkeys resulted in external and skeletal abnormalities.[3] Appropriate contraception should be initiated prior to treatment, during treatment, and for six months after final dose of teprotumumab.[3] Drug discontinuation should occur in the event of pregnancy.[3] Both study protocols were amended to refine definitions of appropriate contraception, duration of contraception after last study dose, and increase frequency of pregnancy monitoring throughout the active study periods.[22,25] The final inclusion criteria for the Douglas et al. study included pregnancy tests at baseline and all study visits through week 48 for women of childbearing potential (those with onset of menopause for less than 2 years or non-therapy-induced amenorrhea for less than 12 months before screening, and not surgically sterile).[25] Additionally, those female participants of childbearing potential who were sexually active with a non-vasectomized male partner were required to use 2 reliable forms of contraception (defined as those with failure rates of <1%) with hormonal contraception recommended as one of those two types for all patients, and initiated one full cycle before the first study infusion and continued for 180 days after the final study infusion.[25] Non-vasectomized male subjects, who were sexually active with a female partner of childbearing potential, agreed to the use of barrier contraceptives from screening until 180 days after the final study infusion.[25]

Table 4. Treatment Emergent Adverse Events[3]

Adverse Reactions	Teprotumumab N=84 N (%)	Placebo N=86 N (%)
Muscle Spasms	21 (25%)	6 (7%)
Nausea	14 (17%)	8 (9%)
Alopecia	11 (13%)	7 (8%)
Diarrhea	10 (12%)	7 (8%)
Fatigue	10 (12%)	6 (7%)
Hyperglycemia	8 (10%)	1 (1%)
Hearing Impairment	8 (10%)	0
Dysgeusia	7 (8%)	0
Headache	7 (8%)	6 (7%)
Dry Skin	7 (8%)	0

* Numbers differ from Table 6 due to receipt of study drug by placebo patient.

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Reduction of TED complications (including vision loss, need for surgery, need for orbital irradiation)
2) Change in Severity of TED
3) Improved Quality of Life
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Composite reduction of proptosis and CAS[1]
2) Reduction of proptosis[2]

Table 5. Pharmacology and Pharmacokinetic Properties[3]

Parameter	
Mechanism of Action	• Binds to IGF-1R, blocking activation and signaling • Mechanism of action in thyroid eye disease not fully characterized
Oral Bioavailability	N/A
Distribution and Protein Binding	• 3.26 ± 0.87 L central VD, 4.32 ± 0.67 L peripherally • Protein binding not reported
Elimination	NR
Half-Life	• 20 ± 5 days • no clinically significant differences based on age (18-80 y), gender, race/ethnicity (103 White, 10 Black, 3 Asian), weight (46-169 kg), renal impairment (mild-moderate using Cockcroft-Gault equation), bilirubin level (2.7-24.3 mcmol/L), AST level (11-221 unit/L), ALT level (7-174 unit/L) • Effect of hepatic impairment unknown
Metabolism	Not fully characterized, anticipated to undergo proteolysis

Abbreviations: ALT = alanine amiotransferase; AST = aspartate aminotransferase; IGF-1R = insulin-like growth factor- 1 receptor; L = liter; mcmol= micromole; N/A = not applicable; NR = not reported; VD = volume of distribution; y = years

Table 6. 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. NCT01868997[1,10,22,23] Smith et al. Phase 2, DB, PC, MC, RCT	1. Placebo (normal saline) IV infusion q3wk over 24 wk for 8 total doses 2. Teprotumumab 10 mg/kg IV infusion x 1, then 20 mg/kg IV infusion q3wk x 7 1:1 randomization Study timeline -Screening (2-6 weeks): 1-3 visits -Intervention (24 weeks-used for primary/secondary endpoints): every 3 weeks	Demographics: -Mean age: PCB 54.2±13.0y Tep 51.6±10.6y -Age >/= 65 y: PCB 20% TEP 9% -Female: PCB: 82% TEP: 65% White: 86% Smoker: PCB 41% TEP 26% -Mean duration of GD: PCB 10.8m (1.2-299.0) TEP 10.7m (1.2-228.0) -Median time since thyroid tx initiation: PCB 15m (3-189)	ITT: 1. 45 2. 42 PP: 1. 36 2. 33 Safety: 1. 44 2. 43 Attrition: 1. 6 (13.3%) 2. 5 (11.9%)	Primary Endpoint:* Responder rate: CAS decrease ≥2 AND Proptosis decrease ≥ 2mm AND no worsening of non-study eye ITT: 1. 9/45 (20%) 2. 29/42 (69%) OR 8.86 (95% CI 3.29 to 23.8) P <0.001 Secondary Endpoints:* Change from Baseline Proptosis (mm) 1. -0.15 ± 0.19 2. -2.46 ± 0.20 P<0.001 CAS (7 point scale)	49%/3 NA	Outcome: Death 1. 0 2. 0 Discontinuation: 1. 6 2. 6 Serious AE: 1. 1 (2%) 2. 5 (12%) Any AE 1. 32 (73%) 2. 32 (74%)	10%/ 10	**Risk of Bias (low/high/unclear)**: Selection Bias: (High) Randomized 1:1 and stratified at each site and smoking status by an interactive web-response system. Significant group imbalances of important variables noted: including; sex, smoking (*despite stratification*), thyroid hormone levels, and time since thyroid tx initiation. Unclear quality of baseline variable assessment [ex. incongruence between history of RAI or surgical thyroidectomy (23%) and those on thyroid replacement (61%); median time since thyroid tx initiation longer than mean duration of GD]. Allocation concealment not described. Performance Bias: (Low) Patients, investigators, and trial-site personnel were blinded. Method to maintain blinding not described. Dispensing pharmacists were

	-Follow-up (48 weeks): every 12 weeks, no additional treatment for at least initial 12 weeks.	TEP 8m (1-134) -Mean duration eye symptoms: PCB 5.2±2.3m TEP 4.7±2.1m Key Inclusion Criteria: - 18 to 75 y old - Clinical dx of GD with active TED with CAS ≥ 4 in more severely affected eye - TED dx ≤ 9 months after onset of symptoms* - Euthyroid (± 50% reference range FT3 and FT4) * - no hx surgical or medical tx (ex. oral methylprednisolone equivalent ≤ 1 g cumulative, 6 wk washout)* -Not requiring immediate ophthalmological surgical intervention -DM controlled by no change medication or insulin >10% in previous 60 days -Neg. pregnancy tests and stringent birth control for women of childbearing potential and men in protocol and 90 days after final study drug administration. See protocol for details* Key Exclusion Criteria: - optic neuropathy - severe ocular surface damage - CAS 2 or more point improvement b/t		1. -1.85 ± 0.17 2. -3.43 ± 0.18 P<0.001 GO-QOL (100 point scale overall and each subscale)† Overall 1. 6.8 ± 2.3 2. 17.7 ± 2.4 P < 0.01 Visual functioning subscale 1. 7.5 ± 2.7 2. 21.7 ± 2.9 P <0.001 Appearance subscale 1. 6.6 ± 2.7 2. 12.9 ± 2.8 P=0.10 Other relevant outcomes[10]: Follow-up period additional therapy with pulse corticosteroids ± rituximab ± orbital decompression 1. 6 (0/6 responders at week 24) 2. 4 (4/4 responders at week 24) Proptosis relapse ≥2 mm in responders week 24 to 72 1. 3/9 2. 11/30 (1/30 TEP had missing value as had orbital decompression at week 70)	NA NA			aware of group assignment and dispensed matched placebo. Detection Bias: (High) Same clinician measured outcomes at each visit for individual patients when possible. Investigators provided training and copies of same resource for CAS for consistency across trial sites. Unclear if proptosis effect may contribute to unblinding and effect size of subjective CAS measures given continuity created by using same observer. GO-QOL was self-administered. Attrition Bias: (Low) Intention to treat analysis used, dropout > 10% but similar between groups. Week 24 data included for all patients, including discontinuations. If week 24 data unavailable, patient was considered to have failed treatment for binary outcomes. No imputation of missing data for secondary endpoints as MMRM model accommodates missing data. Reporting Bias: (High) Significant protocol changes of endpoints near end of study period, though no interim data analysis is reported to have been done. Over emphasis of exploratory endpoints (i.e., onset of response, time course, graded response, patients with CAS of 0 to 1). Other Bias: (High) Manufacturer (River Vision Development, later acquired by Horizon Pharmaceuticals) collaborated on trial design, provided funding, and was responsible for trial oversight. Multiple protocol changes involving important inclusion/exclusion criteria such as clarification of previous steroid medication use and current thyroid status throughout study period. **Applicability**: Patient: Absence of baseline severity limits understanding of patient population treated. Patient population of primarily white patients may not accurately represent Medicaid population or general disease distribution. No data on non-GD induced TED, those with previous treatment with failure, incomplete

		screening and baseline visit -Treatment with oral or IV steroids in previous 3 months except as above. Administration of any other immunosuppressive agent for any indication in the previous 3 months other than topical steroids for dermatologic use* - Previous treatment with rituximab - Hx orbital irradiation						response, or relapse after steroid or other immunosuppressant, or those with sight-threatening disease. Intervention: Dose based on previous oncology dose ranging studies. Inadequate data on repeat dosing, concomitant steroid use, and duration of effects to understand long term benefit. Comparator: Placebo; active comparator against current standard of care (i.e. corticosteroids) lacking Outcomes: Composite containing CAS response (with proptosis response) not considered appropriate by FDA. Proptosis appropriate surrogate. Not designed to study long term reduction of TED induced vision loss. Questions remain from FDA regarding validity of GO-QOL. Setting: 15 sites in US and Western Europe
2. OPTIC NCT 03298867[2,10,25,26] Douglas et al. Phase 3, DB, PC, MC, RCT	1. Placebo (normal saline) IV infusion q3wk over 24 wk for 8 total doses 2. Teprotumumab 10 mg/kg IV infusion x 1, then 20 mg/kg IV infusion q3wk x 7 1:1 randomization Study timeline -Screening: 2-6 weeks prior to baseline -Intervention (24 weeks-used for primary/secondary endpoints): every 3 weeks -Follow-up (48 weeks): proptosis *responders* every 12 weeks, no additional	Demographics: -Mean age: PCB 48.9±13.0y TEP 51.6±12.6y -Age >/= 65 y: PCB 10% TEP 22% -Female: PCB: 74% TEP: 71% White: 87% Smoker (current or former): PCB 19% TEP 22% -Mean duration of GD: PCB 2.2±3.2y TEP 3.5±6.1y -Mean duration TED PCB 6.4±2.4m TEP 6.2±2.3m Key Inclusion Criteria: -18 to 75 y old - Dx of GD	ITT: 1. 42 2. 41 PP: 1. 34 2. 33 Safety: 1. 42 2. 41 Attrition: 1. 2 (4.8%) 2. 2 (4.9%)	Primary Endpoint: Proptosis responder rate: Proptosis ≥ 2mm reduction from baseline ITT: 1. 10% 2. 83% Treatment difference 73.45% (95% CI 59% to 88%) P <0.001 Secondary Endpoints: Overall responder rate: CAS decrease ≥2 AND Proptosis decrease ≥ 2mm AND no worsening of non-study eye 1. 7% 2. 78% Treatment difference 72.46% (95% CI 57.57% to 87.35%) P<0.001 CAS value 0 or 1 (7 point scale): 1. 21% 2. 59%	73%/ 2 71%/ 2 38%/ 3	Outcome: Death 1. 0 2. 0 Discontinuation: 1. 1 2. 1 Serious AE: 1. 1 2. 2 Any AE 1. 29 (69%) 2. 35 (85%)	16%/ 7	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Randomized 1:1 and stratified by tobacco status using interactive web response system. Study groups well balanced. Method of allocation concealment not described. Baseline groups similar. Performance Bias: (Low) Patients, investigators, and trial-site personnel were blinded. Method to maintain blinding not described. Dispensing pharmacists were aware of group assignment and dispensed matched placebo. Detection Bias: (High) Same clinician measured outcomes at each visit for individual patients when possible. Investigators provided training and copies of same resource for CAS for consistency across trial sites. Unclear if proptosis effect may contribute to unblinding and effect size of subjective CAS measures given continuity created by using same observer. GO-QOL was self-administered. Attrition Bias: (Low) Intention to treat analysis and low dropout (<5%). Week 24 data included for all patients, including discontinuations. If week 24 data unavailable,

	treatment for at least initial 12 weeks. <u>-Open-label extension study/NCT03461211:</u> (48 weeks): proptosis *non-responders* or *responders who relapse* from either study group may receive 8 drug infusions as above with additional follow-up.	-Active, moderate-to-severe TED -CAS ≥ 4 in more severely affected eye - ≤ 9 months after onset of ocular symptoms - Euthyroid (± 50% reference range FT3 and FT4) -Not requiring immediate ophthalmological surgical intervention -DM patients must be controlled by having no new medication or change medication or insulin >10% in previous 60 days AND HbA1C <9.0% -Neg. pregnancy tests and stringent birth control requirements for women of childbearing potential and men throughout protocol and 90 days after final study drug administration. See protocol for details. <u>Key Exclusion Criteria</u>: -optic neuropathy -corneal decompensation unresponsive to medical management - Improvement of CAS by 2 or more points or proptosis by 2 mm b/t screening and baseline visit - Hx orbital irradiation -TED treatment with oral steroid cumulative dose ≥ 1 g methylprednisolone equivalent; < 1 g methylprednisolone equivalent cumulative dose requires 6 wk washout		Treatment difference 36.03% (95% CI 17.39% to 54.67%) P<0.001 LS Mean change in measurement of proptosis from baseline:‡ 1. -0.53mm 2. -3.32mm Treatment difference -2.79mm (95% CI -3.4mm to -2.17 mm) P NR GO-QOL (100 point scale overall and each subscale): 1. 1.80 2. 17.28 Treatment difference 15.48 (95% CI 8.43 to 22.53) P NR Diplopia responder rate at wk 24:* 1. 29% (8/28) 2. 68% (19/28) Difference 39% (95% CI 16% to 63%) P=0.001	NA NA			patient was considered to have failed treatment for binary outcomes. No imputation of missing data for proptosis and GO-QOL as MMRM model accommodates missing data. <u>Reporting Bias</u>: (High) Primary and secondary endpoints all reported. Secondary endpoint of diplopia response added by amendment just prior to study completion. No interim data analysis was planned. LS mean average change in proptosis results differed in study publication and FDA review document. Thyroid status reported as group means rather than percentage of patients inside or outside of range, therefore unable to compare level of control between groups & between studies. <u>Other Bias:</u> (High) Manufacturer (Horizon Therapeutics) sponsored trial, designed with input from investigator steering committee, contributed in collection, analysis, and interpretation of data, and in manuscript creation. Trial was conducted with oversight from a contract research organization (Syneos Health). **Applicability**: <u>Patient:</u> Patient population of primarily white patients may not accurately represent Medicaid population or general disease distribution. Inclusion of baseline severity appropriate for study drug. No data on non-GD induced TED, those with previous treatment with failure, incomplete response, or relapse after steroid or other immunosuppressant, or those with sight-threatening disease. <u>Intervention</u>: Dose based on previous oncology dose ranging studies. Inadequate data on repeat dosing, concomitant steroid use, and duration of effects to understand long term benefit. <u>Comparator</u>: Placebo; active comparator against current standard of care (i.e. corticosteroids) lacking

		-Oral steroid use for any indication other than TED in the previous 3 months other than topical steroids for dermatologic use -Selenium or biotin use other than in multivitamin, must be d/c 3 weeks prior to screening - Previous treatment with rituximab or tocilizumab -Other immunosuppressive agent within 3 months of screening -Biopsy-proven or clinically suspected inflammatory bowel disease						Outcomes: Proptosis appropriate surrogate, study not designed to study long term reduction of TED induced vision loss. Questions remain from FDA regarding appropriateness of CAS and validity of GO-QOL tools. Setting: 13 sites in US and Europe

Abbreviations: AE = adverse events; ARR = absolute risk reduction; b/t = between; CAS = Clinical Activity score; CI = confidence interval; DB = double blind/masked; d/c = discontinued; DM = diabetes mellitus; dx = diagnosis; ex = except/exception; FT3 = free triiodothyronine; FT4 = free thyroxine ; GD = Graves' disease; GO-QOL = Graves' Orbitopathy Quality of Life Questionnaire; HbA1c = hemoglobin A1C; hx = history; ITT = intention to treat; IV = intravenous; LS = least squares; mITT = modified intention to treat; m = months; mm = millimeter; MMRM = Mixed Model Repeated Measures; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; OR = Odds ratio; PC = placebo controlled; PCB = placebo; PP = per protocol; RCT = randomized controlled trial; SD = standard deviation; TEP = teprotumumab; tx = treatment; US = United States; wk = week; y = years.
Plus/minus values (±) are mean±SD
*Amended after study initiation[22,25]
†Authors defined "clinical relevance" as a change of at least 8 points.[1,22] A 6 point change is considered clinically relevant and the tool is considered valid by EUGOGO.[21] The FDA had not received validation information and does not interpret GO-QOL scores in NDA application review.[10]
‡Results in table from study publication.[2,26] Values differ in FDA review (PCB -0.5 mm vs TEP -2.8 mm; LSM -2.3 mm, 95% CI -2.8 mm to -1.8 mm).[10]

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Appendix 1: Prescribing Information Highlights

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

TEPEZZA (teprotumumab-trbw) for injection, for intravenous use
Initial U.S. Approval: 2020

----------INDICATIONS AND USAGE----------
TEPEZZA is an insulin-like growth factor-1 receptor inhibitor indicated for the treatment of Thyroid Eye Disease (1)

----------DOSAGE AND ADMINISTRATION----------
- Initiate dosing with 10 mg/kg for first infusion, followed by 20 mg/kg every 3 weeks for 7 additional infusions (2.1)
- Administer TEPEZZA by intravenous infusion over 60 to 90 minutes (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
For Injection: 500 mg lyophilized powder in a single-dose vial for reconstitution (3)

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

----------WARNINGS AND PRECAUTIONS----------
- Infusion reactions: If an infusion reaction occurs, interrupt or slow the rate of infusion and use appropriate medical management (5.1)
- Exacerbation of Preexisting Inflammatory Bowel Disease (IBD) : Monitor patients with preexisting IBD for flare of disease; discontinue TEPEZZA if IBD worsens (5.2)
- Hyperglycemia: Monitor glucose levels in all patients; treat hyperglycemia with glycemic control medications (5.3)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence greater than 5%) are muscle spasm, nausea, alopecia, diarrhea, fatigue, hyperglycemia, hearing impairment, dry skin, dysgeusia and headache (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Horizon at 1-866-479-6742 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
Females of Reproductive Potential: Appropriate forms of contraception should be implemented prior to initiation, during treatment and for 6 months following the last dose of TEPEZZA (8.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 1/2020

Teprotumumab

Goal(s):

- To ensure appropriate use of teprotumumab in patients with Thyroid Eye Disease (TED)

Length of Authorization:

- 8 total lifetime doses (approve for 9 months)

Requires PA:

- Teprotumumab

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. Go to #2	
2. Is the patient an adult (18 years or older)?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the medication being ordered by, or in consultation with, an ophthalmologist or specialized ophthalmologist (e.g. neuro-ophthalmologist or ocular facial plastic surgeon)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Does the patient have **active** TED? • Defined as Clinical Activity Score (CAS) of 4 or higher on 7 point scale within past 3 months.	**Yes:** Go to #5 CAS score:_____ Score date:_____	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
5. Does the patient have **moderate**, **severe**, or **sight-threatening** TED? • Defined by the Graves' Orbitopathy Severity Assessment • Possible severity ratings are mild, moderate, severe, and sight-threatening.	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the patient currently euthyroid (thyroid hormone levels no more than 50% above or below of normal range) within past 3 months?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Does the patient have <u>any</u> of the following: • a contraindication or severe side effect* to corticosteroids <u>or</u> • failed to respond to 6 weeks of low-dose corticosteroid prophylaxis after radioactive iodine treatment <u>or</u> • failed to respond/relapsed after at least 3 weeks of high-dose (IV or oral) corticosteroids *Note: • Teprotumumab is associated with hyperglycemia which may necessitate diabetic medication changes and may not be an appropriate alternative when avoiding steroids in patients with uncontrolled diabetes mellitus.	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
8. Is the patient male or female without childbearing potential? Female without childbearing potential defined as: • Onset of menopause >2 years before current date or • Non-therapy-induced amenorrhea >12 months before current date or • Surgically sterile (absence of ovaries and/or uterus, or tubal ligation) or • Not sexually active	**Yes:** Go to #11	**No:** Go to #9
9. Is there documentation of negative pregnancy test within past 4 weeks?	**Yes:** Go to #10 Type of test (urine or serum): _____ Date of test:_____	**No:** Pass to RPh. Deny; medical appropriateness
10. Has patient been counselled on risk of fetal harm AND agreed to use at least one reliable form of contraceptive for entire duration of drug therapy and for 180 days (6 months) after final dose? • Reliable forms of birth control have less than 1% failure rate/year with consistent and correct use • Examples include: implants, injectables, combined oral/intravaginal/transdermal contraceptives, intrauterine devices, sexual abstinence, or vasectomized partner • Hormonal methods should be started at least one full menstrual cycle prior to initiation of teprotumumab.	**Yes:** Go to #11 Date of Counselling: _____ Contraceptive method:_____	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
11. Has the patient previously received any doses of teprotumumab?	**Yes:** Approve balance to allow 8 total lifetime doses† (8 doses – previous # doses = current approval #) Previous number of doses_____	**No:** Approve 8 doses†

† All approvals will be referred for and offered optional case management

P&T/DUR Review: 12/20 (SF)
Implementation: TBD

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

Drug Class Update: Gout Agents

Date of Review: December 2020

Date of Last Review: January 2017
Dates of Literature Search: 11/01/2016 - 08/15/2020

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

Purpose for Class Update:
The purpose of this class update is to evaluate new evidence for the drugs used in the treatment of gout and update policy if necessary. Specifically, evidence for the role of colchicine in patients with cardiovascular disease (CV) will be reviewed and the evidence for the appropriateness of initiating non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine concomitantly will be evaluated.

Summary of Prior Reviews and Current Policy:
- A drug class update was last preformed in January of 2017 resulting in no changes to the preferred drug list (PDL). High quality evidence supports the use of NSAIDs, colchicine, and systemic corticosteroids for the treatment of acute gout and reduction in serum urate (SU) levels with allopurinol and febuxostat. The use of low-dose colchicine is recommended over high-dose, as similar levels of pain relief have been demonstrated with a lower incidence of adverse reactions. For patients requiring urate lowering therapy (ULT) allopurinol is recommended first-line. Combination therapy with allopurinol and uricosurics is recommended for patients requiring additional therapy to obtain target SU levels. Long-term ULT is not recommended for a majority of patients after the initial attack or in patients with infrequent attacks.
- Allopurinol and a combination product of probenecid/colchicine are preferred therapies in the class. All other gout treatments are subject to prior authorization (PA) criteria.

Research Questions:
1. What is the comparative evidence of efficacy for drug therapies used in the management of gout based on important outcomes such gout flares, SU levels and pain?
2. What is the evidence for harms associated with therapies for the treatment of gout?
3. Are there subpopulations based on co-morbid conditions (i.e., renal insufficiency, peptic ulcer disease) or gout history (i.e., acute versus chronic) in which one drug may be more effective or associated with less harm than other drugs used for prevention of gout flares?
4. What is the evidence for the use of colchicine in cardiovascular disease?
5. Is there evidence for the use of NSAIDs and colchicine concomitantly?

Author: Kathy Sentena, PharmD

Conclusions:

- Two systematic reviews, 4 guidelines and 2 randomized controlled trials (RCT) are included in this evidence review. There was no new evidence for the use of NSAIDs, colchicine, systemic corticosteroids, allopurinol, febuxostat and probenecid for the treatment of gout.

CARDIOVASCULAR

- There is evidence to recommend colchicine for prevention of CV outcomes in patients at high risk for CV events and for those with a recent myocardial infarction (MI) supported by evidence from one systematic review and 2 randomized controlled trials.
    - A Cochrane review found colchicine was not significantly different from controls for mortality (all-cause and CV). Myocardial infarction, mostly non-fatal, was reduced in adult patients, compared to placebo and all other types of comparators (IFN-c 1b, peg-interferon-alpha, aspirin, prednisone, ursodeoxycholic acid, methotrexate, melphalan, dimethyl sulfoxide, and standard care for chronic liver disease [diuretics, beta-blockers, ursodeoxycholic acid]), based on moderate strength of evidence, 12 per 1000 patients vs. 58 per 1000 patients (relative risk [RR] 0.20; 95% confidence interval [CI], 0.07 to 0.57).[1]
    - A good quality, double-blind, placebo-controlled trial in patients with a history of chronic coronary disease found colchicine to reduce the composite primary endpoint of CV death, spontaneous MI, ischemic stroke or ischemic-driven coronary revascularization by 6.8% compared to 9.6% in the placebo group (absolute risk reduction [ARR] 2.8%/ number needed to treat [NNT] 36) (moderate strength of evidence).[2]
    - A good quality trial in patients with a recent MI found colchicine to reduce the composite end-point of death from CV causes, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina leading to coronary revascularization by 5.5% in the colchicine group compared to 7.1% in the placebo group (ARR 1.6% /NNT 63) (moderate strength of evidence).[3]
- There is moderate strength of evidence that colchicine, when combined with a NSAID, is more effective than an NSAID alone at reducing recurrent pericarditis (ARR 23%/NNT 5). Acute pericarditis was reduced with colchicine (in combination with an NSAID) compared to an NSAID alone based on moderate strength of evidence (ARR 22% and NNT of 5).[4]

GOUT

- Evidence from the following guideline updates support the current policy for gout treatments: 2016 American College of Physicians (ACP) guideline, 2017 guideline from the British Society for Rheumatology (BSR) and the 2020 American College of Rheumatology (ACR) guideline on gout management.
- There is a paucity of evidence to guide the use of combination anti-inflammatory therapies in the acute treatment of gout. The BSR recommends the use of an NSAID with a steroid (oral or intra-articular) or colchicine in patients with acute gout who have an insufficient response to monotherapy, which is based on expert opinion due to insufficient evidence.[5]

BEHÇET'S SYNDROME

- A 2018 recommendation from the European League Against Rheumatism (EULAR) on the management of Behçet's Syndrome (BS) recommends the use of colchicine, with or without NSAIDs, for mucocutaneous and arthritic manifestations of BS (high strength of evidence).

Recommendations:

- No changes to the PDL are warranted based on new clinical evidence presented in this review.
- Recommend amending the PA criteria to allow for colchicine use in patients with pericarditis and BS.
- Evaluate costs in executive session.

Background:

Gout is the most common form of inflammatory arthritis.[6] The pathophysiology of gout is a result of rising serum urate levels that exceed the saturation point in the blood leading to crystals that deposit in cartilage, bones, tendons and other sites. This increase in serum urate can be from overproduction or reduced excretion of uric acid resulting in inflammatory joint swelling and pain.[7] The ACR/European League Against Rheumatism (EULAR) classifies gout based on presence of monosodium urate monohydrate (MSU) crystals in the symptomatic joint, bursa or tophi or at least 1 episode of swelling, pain or tenderness in a peripheral joint or bursa with additional clinical criteria also being met.[7] The American College of Physicians (ACP) recommends synovial fluid analysis in patients with acute gout if diagnostic testing is indicated.[8]

Gout is characterized by acute attacks (lasting 7-14 days) that are self-limiting and are accompanied by symptoms of pain and inflammation that often presents in the toe but can occur in other joints. Chronic gout stems from acute attacks that increase in duration and become persistent.[8] Asymptomatic hyperuricemia can also occur; however, there is no evidence to support treatment as a preventative strategy for progression to symptomatic gout.[8] The risk of acute gout attacks can be predicted by serum urate levels. Guidelines recommend serum urate levels less of than 6 mg/dL for patients with gout and less than 5 mg/dL in patients with significant gout.[9] Tophi, which are uric acid crystals that deposit in the joints and other areas, may develop in patients with chronic gout and hyperuricemia. Important outcomes to consider when assessing treatment for gout are: pain, serum and/or uric acid levels, gout attacks, development of tophi, progression from acute to chronic gout and quality of life.

Risk factors for the development of gout include obesity, excessive alcohol intake, dietary factors, medications that increase uric acid levels and chronic kidney disease.[10] It is generally recommended that non-pharmacological therapy, in the way of lifestyle factors, be modified to manage gout, in addition to pharmacotherapy. Patients with a diagnosis of gout are advised to avoid organ meats, high fructose corn syrup-sweetened sodas and other foods, alcohol overuse, and alcohol abstinence during acute gout attacks.[6] Patients are also encouraged to minimize impact of comorbidities by optimizing weight, regular exercise, dietary modifications, minimizing alcohol consumption, and treatment of underlying CV risk factors.[10] Vitamin C supplementation has been suggested but there is no evidence to support its use in the management of gout.[11]

Selection of gout therapies is dependent on the diagnosis of acute or chronic gout (Table 1).[6,10] Treatment for acute gout should be initiated within 24 hours of the onset of the attack. The ACR recommends treatment based on severity of pain and the number of joints involved.[12] Monotherapy with oral NSAIDS, systemic corticosteroids, or colchicine is recommended for mild to moderate severity of acute gout (visual analog score [VAS] of less than 6 and involvement in 1-3 small joints or 1-2 large joints). Combination therapy is indicated for polyarticular attacks with severe pain when monotherapy is insufficient. Combination options are: 1) NSAIDs and colchicine; 2) oral corticosteroids and colchicine; or 3) intra-articular steroids and one of the other oral treatment options.[12] Combination therapy for initial therapy is based on off consensus opinion due to lack of high-quality evidence. In severe refractory cases of gout, use of a biologic interleukin-1 (IL-1) inhibitor can be considered based on moderate strength of evidence.[11] High strength of evidence supports the use of adrenocorticotropic hormone (ACTH) subcutaneous injections as an option in patients who are not able to take medications by mouth.[12,11]

Management of chronic gout focuses on urate reduction through ULT (**Table 1**).[5,13] Guidelines recommend ULT in patients with a gout diagnosis and the following: tophus or tophi, frequent attacks (≥ 2 attacks/year), chronic kidney disease stage 2 or worse or a history of past urolithiasis.[6] Serum urate levels should be checked every 2-5 weeks during the titration phase and every 6 months once a maintenance dose is determined. Xanthine oxidase inhibitors (XOI),

specifically allopurinol followed by febuxostat, are recommended as first-line pharmacological treatment options. Alternative pharmacological options are uricosurics (probenecid).[12] Combination therapy with a XOI and probenecid are recommended if there is an insufficient response to XOI monotherapy.[6] If patients develop an acute gout attack on ULT, recommendations are to continue ULT while treating the acute attack.

Combination therapy with ULT and acute gout medications are recommended for patients experiencing symptoms of an acute attack and are candidates for chronic treatment. Historically, it is recommended that ULT be started 2 weeks after an acute flare subsides, as ULT may increase acute gout attacks initially; however, there is limited evidence that this delay is not required.[6] Low dose colchicine (0.6 mg twice daily) or NSAIDs are recommended first-line for prophylaxis. Low dose prednisone or prednisolone are also used as an alternative to first-line agents in some patients.[5] Prophylaxis is recommended for at least 6 months.

Table 1. Treatments used for the Management of Gout[5,13]

Drug	Mechanism of Action
Acute Gout Management	
NSAIDs†	Anti-inflammatory
Corticosteroids (intraarticular or oral†)	Anti-inflammatory
Colchicine†	Anti-microtubule disrupting agent/anti-inflammatory
Pituitary adrenocorticotropic hormone (ACTH)	Anti-inflammatory
Urate-lowering therapy (ULT)	
Allopurinol	Xanthine oxidase inhibitor
Febuxostat	Xanthine oxidase inhibitor
Probenecid	Uricosuric - prevention of renal reabsorption of uric acid and increased excretion
Abbreviations: NSAID – non-steroidal anti-inflammatory drugs Key: † Also recommended for gout prophylaxis	

Off-label Colchicine Uses

There is limited evidence for the use of colchicine in the treatment of pericarditis. Pericarditis is an inflammatory condition of the pericardium, a membrane that surrounds the heart. Recurrent pericarditis causes severe chest pain and is a common complication of acute pericarditis. The underlying etiology of pericarditis is often viral or idiopathic. European Society of Cardiology (ESC) recommends combination treatment with NSAIDs (for approximately two weeks) and colchicine (for approximately 3 months for acute pericarditis and at least 6 months for recurrent pericarditis) for the treatment of acute and recurrent pericarditis.[14] Glucocorticoids can be used as an alternative if patients have contraindications to NSAIDs.

Colchicine is used off-label for the treating BS. Behçet's Syndrome is an inflammatory syndrome that often presents with recurrent oral aphthous ulcers in addition to systemic manifestations, such as joint involvement and arthritis.[15] BS has a relapsing remitting component which is most commonly treated with anti-inflammatories to suppress inflammatory exacerbations. Standards of care include the use of colchicine, 1-2 mg/day (divided) as a first-line treatment option for recurrent oral or genital ulcers and for arthritic manifestations, with or without NSAIDs.[15]

There are approximately 6,000 patients in the Fee-for-Service population with the diagnosis of gout and only about 70 with BS. The overall costs for the class do not represent a large expenditure for the Oregon Health Plan (OHP). PDL compliance is around 80%.

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

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

New Systematic Reviews:

Colchicine Use for Cardiovascular Indications

Cochrane – Colchicine for Prevention of Cardiovascular Events
A 2016 Cochrane review evaluated the evidence for the use of the anti-inflammatory colchicine on prevention of CV outcomes in adult patients, especially patients with high CV risk.[1] Recent studies have noted a benefit with low-dose colchicine on CV outcomes; however, previous evidence has not demonstrated a CV benefit. Thirty-nine trials (n=4,992) were included in the analysis. Most trials were small, single-center studies with placebo comparators. Active treatment comparisons consisted of the following: IFN-c 1b, peg-interferon-alpha, aspirin, prednisone, methotrexate, melphalan, dimethyl sulfoxide, and standard care for chronic liver disease (diuretics, beta-blockers, ursodeoxycholic acid). Four trials focused specifically on the use of colchicine in the CV setting (e.g., in patients with diabetes, undergoing stent implantation, heart failure [HF], coronary artery disease [CAD] or after angioplasty). The most commonly studied colchicine dose used in the 69% of the trials was 1 mg/day or less and 1.2 mg/day in the remaining trials. CV endpoints were not the primary endpoints of most of the included trials. The risk of bias was often considered unclear due to trial methodology used in older trials. The primary outcomes of interest were all-cause mortality, MI, and adverse events.

There is moderate strength of evidence that colchicine had no effect on all-cause mortality compared to any control treatment over a period of 0.5 to 14 years, 182 per 1000 patients vs. 193 per 1000 patients (RR 0.94; 95% CI, 0.82 to 1.09).[1] In a subgroup analysis of patients with high CV risk (secondary prevention of CV disease events, established coronary heart disease) there also was no difference in all-cause mortality (RR 0.54; 95% CI, 0.26 to 1.14) (moderate strength of evidence). Moderate strength of evidence demonstrated that there was also no significant effect of colchicine on CV mortality compared to any control over a period of 0.5 -14 years (RR 0.34; 95% CI, 0.09 to 1.21).[1] Findings were consistent for CV mortality in patients with high CV risk, based on low strength of evidence (RR 0.25; 95% CI, 0.02 to 2.66).[1] There was no difference in findings between colchicine and type of control treatment used. Further research is needed to establish whether colchicine reduces CVD mortality.

There was moderate strength of evidence of a benefit with colchicine, compared to any control, on reducing the risk of MI (mostly non-fatal) over a 3 year period. The incidence of MI was 12 per 1000 patients with colchicine vs. 58 per 1000 patients with controls (RR 0.20; 95% CI, 0.07 to 0.57). In a subgroup analysis, patients at high CV risk had 18 MIs per 1000 patients with colchicine vs 72 per 1000 patients in the control group (RR 0.20; 95% CI, 0.07 to 0.57).[1] Evidence on MI risk was mostly from a single study. Evidence was insufficient for meaningful conclusions to be drawn from data on HF risk and stroke risk.

In summary, there is CV benefit, especially on reducing the risk of MI, with the use of colchicine; however, additional evidence is needed to confirm treatment benefit (See randomized clinical trials presented below). Evidence was downgraded due to imprecision of trial results and missing outcome data for many of the studies.

Cochrane – Colchicine for Pericarditis

There is some evidence to suggest that colchicine is effective in preventing reoccurring pericarditis.[4] A Cochrane review searched evidence up to August 2014 for evidence of effectiveness of colchicine (0.5 mg twice daily) in adult patients with acute or recurrent pericarditis. Four trials met inclusion criteria which included 564 participants. Seventy-seven percent of patients had idiopathic pericarditis. All trials compared colchicine to NSAIDs (e.g., ibuprofen, aspirin, or indomethacin). The primary outcome was time to pericarditis recurrence. Pericarditis was defined as chest pain with (ECG changes +/- echocardiographic changes +/- raised inflammatory markers).

Recurrent pericarditis was reduced in patients treated with colchicine (combined with NSAIDs) compared to NSAIDs alone in trials with a median duration of 18 months based on moderate strength of evidence (HR 0.37; 95% CI, 0.24 to 0.58/NNT 4).[4] Recurrent pericarditis, was reduced with colchicine (in combination with an NSAID) compared to an NSAID alone at 6 months, 137 cases per 1000 patients vs. 490 per 1000 patients (RR 0.28; 95% CI, 0.17 to 0.47) (moderate strength of evidence).[4] At 12 months the reduction in pericarditis risk was maintained (RR 0.36; 95% CI, 0.23 to 0.56) and also at 18 months (RR 0.38; 95% CI, 0.25 to 0.58) (moderate strength of evidence for both).[4] At 18 months the ARR between groups was 23% with an NNT of 5.[4]

There was moderate strength of evidence that colchicine (in combination with NSAIDs) reduced reoccurring acute pericarditis compared to NSAIDs alone with a HR of 0.40 (95% CI, 0.27 to 0.61).[4] Colchicine (combined with an NSAID) compared to an NSAID alone, reduced the recurrence rate of pericarditis in patients with acute pericarditis at 6 months based on moderate strength of evidence (RR 0.36; 95% CI, 0.23 to 0.58).[4] Moderate strength of evidence demonstrated similar results at 12 months (RR 0.40; 95% CI, 0.26 to 0.61) and at 18 months (RR 0.41; 95% CI, 0.28 to 0.61).[4] The ARR between groups was 22% with an NNT of 5.[4]

There was low quality of evidence that colchicine (in combination with an NSAID) provided more symptom relief of pericarditis compared to NSAIDs alone (RR 1.40; 95% CI, 1.26 to 1.56).[4] There was low strength of evidence that adverse effects were not different between groups.

In summary, colchicine (in combination with an NSAID) was more effective than NSAIDs alone in preventing pericarditis recurrence in patients with reoccurring pericarditis or in acute pericarditis. There were only a few participants enrolled in the trials with resistant multiple recurrences, limiting external validity to this population.

Randomized Controlled Trials:
A total of ninety-one citations were manually reviewed from the initial literature search. After further review, eighty-nine citations were excluded because of wrong study design (eg, observational), or outcome studied (eg, non-clinical). Two trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

There is evidence for the use of colchicine in patients with coronary disease and recent MI from two good quality, double-blind, randomized, placebo controlled trials in comparing colchicine 0.5 mg daily to placebo (**Table 2**).[2,3] In first trial, patients had a history of chronic coronary disease and a majority were at least 24 months from having an acute coronary procedure. Patients were optimized on maintenance medications for chronic coronary disease (e.g., statin and lipid lowering agents) and baseline characteristics were well-matched. Incidence rates, based on the composite primary endpoint of CV death, spontaneous (non-procedural) myocardial infarction, ischemic stroke or ischemic-driven coronary revascularization were reduced with colchicine with incidence rates of 2.5 events per 100 person-years compared to 3.6 events per 100 person-years with placebo (**Table 2**).[2] Reductions in composite endpoint was driven by MI events, 3.0% in colchicine treated patients compared to 4.2% in patients treated with placebo (P=0.01/ARR 1.2%/NNT 84). Death from any cause or CV death was not different between groups.

In the second trial, the use of colchicine compared to placebo was studied in adult patients with a recent history of MI (within 30 days before enrollment, mean of 13.5 days), had completed any planned percutaneous revascularization procedures and were treated according to national guidelines.[3] Patients with heart failure (HF), a left ventricular ejection fraction less than 35% or stroke within the previous 3 months were excluded. A majority of patients were on aspirin, a different antiplatelet agent and statin. The primary endpoint, composite of death from CV causes, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina leading to coronary revascularization, was reduced in patients taking colchicine compared to placebo, ARR 1.6%/NNT 63 (**Table 2**).[3] The composite endpoint was driven by MI events, 3.8% in patients treated with colchicine compared to 4.1% treated with placebo (HR 0.91; 95% CI, 0.68 to 1.21; P>0.05).[3] All-cause death and death from CV causes was not different between groups.

Table 2. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Nidorf, et al[2] Phase 3, DB, RCT 28.6 months	Colchicine 0.5 mg once daily Vs. Placebo once daily	Adult patients (35-82 years) with chronic coronary disease (n=5522)	Composite of CV death, spontaneous (non-procedural) myocardial infarction, ischemic stroke or ischemic-driven coronary revascularization	Colchicine: 187 (6.8%) Placebo: 264 (9.6%) HR 0.69 (95% CI, 0.57 to 0.83) P<0.001 ARR 2.8% / NNT 36
Tardif, et al[3] Phase 3, DB, RCT 22.6 months	Colchicine 0.5 mg daily Vs. Placebo daily	Adult patients with MI within 30 days of enrollment, had completed planned percutaneous	Composite end-point of death from CV causes, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina leading to coronary revascularization	Colchicine: 131 (5.5%) Placebo: 170 (7.1%) HR 0.77 (95% CI, 0.61 to 0.96) P= 0.02 ARR 1.6% / NNT 63

		revascularization procedures and were treated according to national guidelines, including intensive use of statins (n=4745)		

Abbreviations: ARR = absolute risk reduction; CI = confidence interval; CV = cardiovascular; DB = Double-blind; HR = hazard ratio; MI = myocardial infarction; NNT = number needed to treat; RCT = randomized clinical trial

After review, 11 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).[16–20,20–26]

New Guidelines:
High Quality Guidelines:

GOUT

American College of Rheumatology – Management of Gout
The 2012 guidance of the management of gout was updated by the ACR in 2020.[11] The objective of the guidance is to provide recommendations on the management of gout as it pertains to: ULT, gout flare management and lifestyle and other medication recommendations. Recommendations are applicable to patients with gout and those with asymptomatic hyperuricemia (≥ 6.8 mg/dl with no prior gout flares or subcutaneous tophi).[11] Guideline methodology was clearly described and 26% of the authors had declared conflicts of interest. Network meta-analyses, with their inherent limitations, were used to determine the effects of starting ULT versus no ULT and for the use of different anti-inflammatory agents in the management of gout flares.

The ACR provided pharmacological recommendations for the management of gout, divided into 4 categories: indications for pharmacological ULT, choice of initial ULT, recommendations pertaining to specific ULT medications and gout flare management.[11] Recommendations are outlined in **Table 3**. For patients that are appropriate candidates, and currently taking ULT, dose titration should be guided by SU values (strongly recommended; moderate strength of evidence). A SU goal and attainment should be < 6 mg/dl when on ULT. Indefinitely using ULT is recommend over stopping it based on very low quality evidence and a conditional recommendation. Guidance on switching ULT is outlined in **Table 4**.

For specific patient subgroups, alternative ULT recommendations are in place. For patients who are of Southeast Asian decent or African America, an HLA-B*5801 test should be conducted before initiating allopurinol therapy but not for other patient populations (very low strength of evidence).[11] Desensitization is

recommended for patients with a prior allergic reaction to allopurinol who cannot be treated with other oral ULTs (very low strength of evidence). Moderate quality evidence suggests that patients with a history of CVD or a new CV event that are taking febuxostat should be switched to an alternative ULT if appropriate. Urine uric acid concentrations are not recommended for patients taking uricosurics, or considering taking uricosurics (very low quality of evidence).[11]

Table 3. ACR Management of Gout Recommendations[11]

Recommendations	Strength of Evidence	Strength of Recommendation
Indications for ULT		
1. ULT should be initiated in patients with 1 or more subcutaneous tophi	High	Strong
2. Patients with radiographic damage attributable to gout should have ULT initiated	Moderate	Strong
3. Patients that experience frequent gout flares (> 2/year) should have ULT initiated	High	Strong
4. For patients with a history of flares (>1) but experience infrequent flares (<2/year), ULT is recommended	Moderate	Conditional
5. Patients with their first flare **should not** receive ULT, except for patients described below	Moderate	Conditional
A. Patients with their first flare and CKD stage ≥3, SU >9 mg/dl, or urolithiasis	Very low	Conditional
6. For patients with asymptomatic hyperuricemia (SU >6.8 mg/dl), with no prior gout flares or subcutaneous tophi, ULT **should not** be initiated	High	Conditional
Choice of Initial ULT in Patients with Gout		
7. Allopurinol is recommended over other ULTs as the first-line therapy (including patients with CKD ≥3)	Moderate	Strong
8. XOIs are recommended over probenecid for patients CKD ≥ 3	Moderate	Strong
9. Initiating allopurinol and febuxostat should be done at low doses with the intent of dose titration (e.g., ≤ 100 mg/day for allopurinol [lower in patients with CKD] or ≤ 40 mg/day for febuxostat)	Moderate	Strong
10. Probenecid should be started at a lower dose (e.g., 500 mg once or twice daily) with dose titration	Moderate	Conditional
11. Concomitant anti-inflammatory* (e.g., colchicine, NSAIDs, prednisone/prednisolone) prophylaxis should be initiated over no prophylaxis	Moderate	Strong
12. Prophylaxis should be continued for 3-6 months rather than < 3 months†	Moderate	Strong
13. If ULT is indicated during a gout flare, it is recommended that ULT be initiated during the flare instead of waiting till the flare has resolved	Moderate	Conditional
14. Pegloticase **should not** be used as a first-line therapy	Moderate	Strong
Gout Flare Management		
15. Patients with gout flares should be managed with colchicine, NSAIDs, or glucocorticoids (oral, intraarticular, or intramuscular)* first-line versus IL-1 inhibitors or ACTH	High	Strong
16. If colchicine is initiated, low-dose (0.6 mg twice daily) versus high-dose should be used	Moderate	Strong

17. Patients with a gout flare who are unable to tolerate, or therapies are contradicted, an IL-1 inhibitor is recommended over no therapy	Moderate	Conditional
18. Patients who are unable to tolerate oral therapy should receive glucocorticoids (intramuscular, intravenous, or intraarticular) over IL -1 inhibitors or ACTH	High	Strong
19. Topical ice can be used during a gout flare if desired as an adjuvant treatment	Low	Conditional
Abbreviations: ACTH - adrenocorticotropic hormone; CKD – chronic kidney disease; IL-1 – interleukin type 1; NSAIDs – non-steroidal anti-inflammatory drugs; SU – serum urate; ULT – urate lowering therapy; XOI – xanthine oxidase inhibitors Key: * Specific patient characteristics should guide anti-inflammatory choice, † Continual evaluation is warranted and continued prophylaxis may be needed if patient continues to have flares		

Table 4. ACR Guidance for Switching to a New ULT[11]

Recommendation	Strength of Evidence	Strength of Recommendation
1. For patients on first maximally tolerated dose XOI monotherapy or FDA-indicated dose and are not at SU target and/or have continuation of frequent gout flares or nonresolving subcutaneous tophi it is recommended that the patient be switched to and alternative XOI over adding a uricosuric therapy	Very low	Conditional
2. Patients who have not achieved SU targets on an XOI, uricosurics and other interventions, with gout and frequent gout flares, or nonresolving subcutaneous tophi, pegloticase is recommended over continuing current ULT	Moderate	Strong
3. Continuing current ULT therapy versus switching to pegloticase is recommended for the following patients with gout: - XOI, uricosurics and other interventions have failed to lower SU to target AND - Have infrequent gout flares (< 2 flares/year) AND - No tophi	Moderate	Strong
Abbreviations: FDA – Food and Drug Administration; SU – serum urate; ULT – urate lowering therapy; XOI – xanthine oxidase inhibitors		

<u>American College of Physicians – Management of Acute and Recurrent Gout</u>

A clinical practice guideline on gout management in adults was published from ACP in 2020 to assist primary care practitioners.[9] The guidance is based off a recent systematic review and meta-analysis performed and funded by Agency for Healthcare Research and Quality (AHRQ). Twenty-eight studies provided evidence for the pharmacological therapies used in the treatment of gout.

The treatment recommendations are described in **Table 5**.[9] Acute gout pharmacotherapy recommendations pertain to colchicine, NSAIDs and corticosteroids. Recommendations for colchicine were based on high-quality evidence that colchicine reduces pain. Moderate-quality evidence found low-dose colchicine (1.2 mg initial dose followed by 0.6 mg in 1 hour) are as effective as higher colchicine doses (1.2 mg initially followed by 0.6 mg/hr for 6 hours). Low-dose colchicine

provided similar pain relief to that of high-dose with a lower incidence of gastrointestinal adverse reactions.[9] Evidence for NSAIDs supported their use in gout as a pain reliever and for prevention of gout flares during urate-lowering therapy. The most common adverse reaction associated with NSAIDs are gastrointestinal, ranging from dyspepsia to bleeding ulcers. The recommendation for corticosteroids ability to reduce pain in patients with acute gout comes from high-quality indirect evidence. Finding for corticosteroids are similar to NSAIDs in time to resolution of symptoms, clinical joint status, or pain reduction.

Evidence demonstrating reduction in SU results from urate lowering therapy (allopurinol and febuxostat) came from 4 RCTs.[9] Lowering of SU was not associated with a reduction in gout attacks within the first 6 months of treatment; however, observational and retrospective cohort studies have shown lower SU levels results in in fewer gout flares. In a comparative effectiveness analysis between allopurinol and high-dose febuxostat (120 mg or 240 mg a day), febuxostat had a higher incidence of gout flares compared to patients treated with allopurinol (100-300 mg a day).[9] Febuxostat (40 mg daily) and allopurinol (300 mg daily) lowered SU levels to the same degree, while febuxostat 80 mg daily was more effective than allopurinol.[9] Lower doses of febuxostat (40 mg and 80 mg a day) and allopurinol had similar efficacy in the number of gout flares. Rash is the most common adverse reaction associated with allopurinol and abdominal pain, diarrhea and musculoskeletal pain with febuxostat. Prophylaxis with low-dose colchicine (0.6 mg twice daily) or NSAIDs demonstrated a reduced risk for gout attacks in patients starting ULT with durations of therapy beyond 8 weeks being more effective than shorter durations of treatment. There is insufficient evidence to recommend treating patients to a target SU level or for specific criteria to guide ULT discontinuation.[9]

Table 5. ACP Guideline Recommendations for Gout Management[9]

Recommendation	Strength of Recommendation	Quality of Evidence
1. Corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), or colchicine should be used to treat patients with acute gout	Strong	High
2. Low-dose colchicine (0.6 mg twice daily) should be used to treat acute gout	Strong	Moderate
3. Long-term urate lowering therapy is not recommended for most patients after a first gout attack or in patients with infrequent attacks.	Strong	Moderate
4. The benefits, harms, costs, and individual preferences should be discussed with patients before initiating urate-lowering therapy, including concomitant prophylaxis, in patient with recurrent gout attacks.	Strong	Moderate

<u>British Society for Rheumatology – Management of Gout</u>

The BSR updated guidelines for the management of gout in adults in 2017. This guidance updates to the 2007 recommendations.[5] The guideline is accredited by the National Institute for Health and Care Excellence (NICE) meeting high-quality methodology standards. Literature was searched from 1974 to June 2015. Level of evidence was graded as described in **Table 6**. Recommendations pertaining to pharmacological management are discussed below. Treatment of acute gout attacks should be treated upon presentation, with an emphasis on continuing established ULT if appropriate.

Table 6. British Society of Rheumatology Level of Evidence Determination[5]

Level of Evidence
1a) meta-analysis of randomized controlled trials
1b) at least one randomized controlled trial

IIa) at least one well-designed controlled study without randomization
IIb) at least one well-designed quasi-experimental study
III) at least one non-experimental descriptive study (e.g., comparative correlation or case-control study)
IV) expert committee reports, opinions and/or experience of respective authorities

Acute Gout

Recommendations for the treatment of acute gout are consistent with other guidelines. Colchicine (0.5 mg once or twice daily) or NSAIDs, at maximum dose, are recommended first-line if there are no contraindications (Ia level of evidence [LoE]). Patients taking NSAIDs or cyclooxygenase-2 inhibitors should also take a gastroprotective agent. An alternative to colchicine and NSAIDs includes joint aspiration and injection of a corticosteroid, especially in monoarticular gout (IV LoE). Combination therapy for acute gout with NSAIDs with corticosteroids or colchicine can be used when the response to monotherapy is suboptimal (V LoE). Patients who do not respond to standard treatment of acute gout may be considered for IL-1 inhibitors (canakinumab, anakinra and rilonacept); however, this therapy recommendation is not approved by the National Institute for Health and Care Excellence (NICE) due to uncertainty of efficacy and safety evidence.

Urate-lowering Therapies

In contrast to the ACR recommendations, the BSR recommends that all patients who have a diagnosis of gout should be offered ULT. Urate lowering therapy should be highly considered for patients who have 2 or more gout attacks in 12 months, tophi, chronic gouty arthritis, joint damage, renal impairment (estimate glomerular filtration rate of 60 ml/min or less), history of urolithiasis, diuretic therapy use, or primary gout starting at a young age (Ia LoE for all except urolithiasis [III LoE] and diuretics and young age [IV LoE]). The guideline recommends discussing ULT with the patients when inflammation is under control and without pain; however, in patients with frequent attacks, it may be appropriate to initiate ULT before resolution of inflammation (IV LoE). The BSR recommends target a SU level of less than 300 µmol/l with ULT to prevent the formation of further urate crystals. A higher SU level can be targeted (360 µmol/l) after tophi have resolved and the patient is symptom free (III and IV LoE). First-line ULT recommendation is for allopurinol (50-100 mg daily) titrated every 4 weeks by a 100 mg until target SU has been reached (Ib LoE). Patients with renal impairment should be have doses titrated by 50 mg every 4 weeks (III LoE). Febuxostat 80 mg daily is a second-line option for ULT, that can be titrated to 120 mg daily if needed (Ia LoE). If XOIs are not tolerated, an alternative therapy option is a uricosuric agent (e.g., probenecid 500-2000 mg daily) (Ia LoE). Patients who have hyperlipidemia and hypertension may be candidates for losartan or fenofibrate, as they have weak uricosuric properties, as does Vitamin C supplements (III LoE). Patients who do not reach SU targets can be given combination therapy with an uricosuric agent and XOI (III LoE).

Prophylaxis

For prophylaxis against acute gout attacks, when ULT is initiated or titrated, colchicine (0.5 mg daily or twice daily) should be offered (Ib LoE). An NSAID, with a gastroprotectant, can be offered as an alternative in patients who are not able to tolerate colchicine (Ib LoE).

Special Populations

Renal Insufficiency: In acute gout, the dose of colchicine should be reduced in patients with an estimated glomerular filtration rate (eGFR) of 10-50 ml/min/1.73 m^2 and not used if the eGFR is 10 ml/min/1.73 m^2 or less. NSAIDs are also not recommended in patients with moderate to severe renal impairment and the patient should be considered a candidate for corticosteroid use.

Severe Refractory Tophaceous Gout: A rheumatologist should be consulted if a patient has severe symptomatic tophaceous gout in which SU cannot be controlled by ULT as monotherapy or in combination therapy. Pegloticase may be an option for these patients, although not approved by NICE.

Pregnancy: NSAIDs can be used in the second trimester in patients who are pregnant with gout. Steroids can be an alternative option. There is no data on allopurinol or febuxostat in pregnancy and they should not be used. Probenecid has been used as an antibiotic in pregnant patients without adverse effects.

BEHÇET'S SYNDROME

EULAR – Management of Behçet's Syndrome

EULAR provided recommendations for the management of BS in a 2018 recommendation statement.[27] EULAR followed the Appraisal of Guidelines Research and Evaluation instrument for development. Endorsed recommendations met inclusion criteria according to the AGREE tool as being high-quality guidance. Recommendations are graded from A-D, A is based on category I evidence and D corresponds to category IV evidence.

Recommendations for the management of BS, as they pertain to medications also used for gout, are presented (**Table 7**).[27] The anti-inflammatory, colchicine, has a role in BS because of the relapsing and remitting course of BS caused by inflammatory exacerbations, which if not managed can lead to irreversible organ damage. The use of colchicine 1-2 mg daily for mucocutaneous lesions and arthritis was used in trials. Improvement in mucocutaneous lesions, complete remission in mucocutaneous lesions and arthritis, and improvement in the Iranian Behçet's Disease Dynamic Activity Measure (IBDDAM) score provided evidence for the use of colchicine in BS. [28]

Table 7. EULAR Recommendations for the Management of Behçet's Syndrome Pertaining to Colchicine Use[27]

Recommendation	Level of Evidence	Strength of Recommendation
Mucocutaneous Involvement		
Colchicine should be used first-line for the prevention of recurrent mucocutaneous lesions, especially for erythema nodosum or genital ulcer	IB	A
Joint Involvement		
Colchicine is recommended first-line for the treatment of BS patients with acute arthritis	IB	A
Abbreviations: BS - Behçet's Syndrome		

After review, one guideline was excluded due to poor quality.[13]

New Formulations or Indications:
None identified.

New FDA Safety Alerts:

Table 8. 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)
Allopurinol[29]	ALOPRIM	8/28/2020	Warnings	Serious and fatal dermatological reactions, including toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in approximately 5 in 10,000 patients (0.05%). Exfoliative, urticarial and purpuric lesions; generalized vasculitis and irreversible hepatotoxicity have also been reported. Patients with the HLA-B*58:01 allele are at higher risk of allopurinol hypersensitivity syndrome (AHS). Consider testing for the allele in genetically at-risk populations. Do not use allopurinol in patients with the HLA-B*58:01 allele unless the benefit clearly outweighs the risk. Patients with renal impairment, especially in those receiving thiazide diuretics may be at increased risk of hypersensitivity reactions.
Febuxostat[30]	ULORIC	2/21/2019	Boxed warning	Increased risk of cardiovascular death in patients with gout and established cardiovascular disease taking febuxostat compared to those taking allopurinol

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
allopurinol	ALLOPURINOL	TABLET	Y
allopurinol	ZYLOPRIM	TABLET	Y
probenecid/colchicine	PROBENECID-COLCHICINE	TABLET	Y
colchicine	COLCHICINE	CAPSULE	N
colchicine	MITIGARE	CAPSULE	N
colchicine	GLOPERBA	SOLUTION	N
colchicine	COLCHICINE	TABLET	N
colchicine	COLCRYS	TABLET	N
febuxostat	FEBUXOSTAT	TABLET	N
febuxostat	ULORIC	TABLET	N
probenecid	PROBENECID	TABLET	N
allopurinol sodium	ALLOPURINOL SODIUM	VIAL	
allopurinol sodium	ALOPRIM	VIAL	
pegloticase	KRYSTEXXA	VIAL	
rasburicase	ELITEK	VIAL	

Appendix 2: Abstracts of Comparative Clinical Trials

Colchicine in Patients with Chronic Coronary Disease

Nidorf SM. Aernoud T L Fiolet , Arend Mosterd , John W Eikelboom , Astrid Schut , Tjerk S J Opstal , Salem H K The, Xiao-Fang Xu , Mark A Ireland, Timo Lenderink , Donald Latchem , Pieter Hoogslag , Anastazia Jerzewski , Peter Nierop , Alan Whelan , Randall Hendriks , Henk Swart , Jeroen Schaap , Aaf F M Kuijper , Maarten W J van Hessen , Pradyot Saklani , Isabel Tan , Angus G Thompson , Allison Morton , Chris Judkins , Willem A Bax , Maurits Dirksen , Marco M W Alings , Graeme J Hankey , Charley A Budgeon , Jan G P Tijssen , Jan H Cornel , Peter L Thompson , LoDoCo2 Trial Investigators

Abstract

Background: Evidence from a recent trial has shown that the antiinflammatory effects of colchicine reduce the risk of cardiovascular events in patients with recent myocardial infarction, but evidence of such a risk reduction in patients with chronic coronary disease is limited.

Methods: In a randomized, controlled, double-blind trial, we assigned patients with chronic coronary disease to receive 0.5 mg of colchicine once daily or matching placebo. The primary end point was a composite of cardiovascular death, spontaneous (nonprocedural) myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization. The key secondary end point was a composite of cardiovascular death, spontaneous myocardial infarction, or ischemic stroke.

Results: A total of 5522 patients underwent randomization; 2762 were assigned to the colchicine group and 2760 to the placebo group. The median duration of follow-up was 28.6 months. A primary end-point event occurred in 187 patients (6.8%) in the colchicine group and in 264 patients (9.6%) in the placebo group (incidence, 2.5 vs. 3.6 events per 100 person-years; hazard ratio, 0.69; 95% confidence interval [CI], 0.57 to 0.83; P<0.001). A key secondary end-point event occurred in 115 patients (4.2%) in the colchicine group and in 157 patients (5.7%) in the placebo group (incidence, 1.5 vs. 2.1 events per 100 person-years; hazard ratio, 0.72; 95% CI, 0.57 to 0.92; P = 0.007). The incidence rates of spontaneous myocardial infarction or ischemia-driven coronary revascularization (composite end point), cardiovascular death or spontaneous myocardial infarction (composite end point), ischemia-driven coronary revascularization, and spontaneous myocardial infarction were also significantly lower with colchicine than with placebo. The incidence of death from noncardiovascular causes was higher in the colchicine group than in the placebo group (incidence, 0.7 vs. 0.5 events per 100 person-years; hazard ratio, 1.51; 95% CI, 0.99 to 2.31).

Conclusions: In a randomized trial involving patients with chronic coronary disease, the risk of cardiovascular events was significantly lower among those who received 0.5 mg of colchicine once daily than among those who received placebo. (Funded by the National Health Medical Research Council of Australia and others; LoDoCo2 Australian New Zealand Clinical Trials Registry number, ACTRN12614000093684.).

Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction

Jean-Claude Tardif, M.D., Simon Kouz, M.D., David D. Waters, M.D., Olivier F. Bertrand, M.D., Ph.D., Rafael Diaz, M.D., Aldo P. Maggioni, M.D., Fausto J. Pinto, M.D., Ph.D., Reda Ibrahim, M.D., Habib Gamra, M.D., Ghassan S. Kiwan, M.D., Colin Berry, M.D., Ph.D., José López-Sendón, M.D., et al

B A C K G R O U N D

Experimental and clinical evidence supports the role of inflammation in atherosclerosis and its complications. Colchicine is an orally administered, potent antiinflammatory medication that is indicated for the treatment of gout and pericarditis.

METHODS
We performed a randomized, double-blind trial involving patients recruited within 30 days after a myocardial infarction. The patients were randomly assigned to receive either low-dose colchicine (0.5 mg once daily) or placebo. The primary efficacy end point was a composite of death from cardiovascular causes, resuscitated cardiac arrest, myocardial infarction, stroke, or urgent hospitalization for angina leading to coronary revascularization. The components of the primary end point and safety were also assessed.
RESULTS
A total of 4745 patients were enrolled; 2366 patients were assigned to the colchicine group, and 2379 to the placebo group. Patients were followed for a median of 22.6 months. The primary end point occurred in 5.5% of the patients in the colchicine group, as compared with 7.1% of those in the placebo group (hazard ratio, 0.77; 95% confidence interval [CI], 0.61 to 0.96; P=0.02). The hazard ratios were 0.84 (95% CI, 0.46 to 1.52) for death from cardiovascular causes, 0.83 (95% CI, 0.25 to 2.73) for resuscitated cardiac arrest, 0.91 (95% CI, 0.68 to 1.21) for myocardial infarction, 0.26 (95% CI, 0.10 to 0.70) for stroke, and 0.50 (95% CI, 0.31 to 0.81) for urgent hospitalization for angina leading to coronary revascularization. Diarrhea was reported in 9.7% of the patients in the colchicine group and in 8.9% of those in the placebo group (P=0.35). Pneumonia was reported as a serious adverse event in 0.9% of the patients in the colchicine group and in 0.4% of those in the placebo group (P=0.03).
CONCLUSIONS
Among patients with a recent myocardial infarction, colchicine at a dose of 0.5 mg daily led to a significantly lower risk of ischemic cardiovascular events than placebo. (Funded by the Government of Quebec and others; COLCOT ClinicalTrials.gov number, **NCT02551094. opens in new tab**)

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to August 19, 2020

Search Strategy:

#	Searches	Results
1	Allopurinol/	7612
2	probenacid.mp.	2
3	colchicine.mp. or Colchicine/	20438
4	febuxostat.mp. or Febuxostat/	946
5	pegloticase.mp.	158
6	rasburicase.mp.	428
7	1 or 2 or 3 or 4 or 5 or 6	28781
8	limit 7 to (english language and humans and yr="2016 -Current")	1896
9	limit 8 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	91

Appendix 4: Key Inclusion Criteria

Population	Patients with acute and chronic gout, recent MI, pericarditis or Behçet's Syndrome
Intervention	Gout drugs
Comparator	Active comparators or placebo
Outcomes	Pain reduction, prevention of recurrent inflammatory condition, prevention of recurrent pericarditis, prevention of CV events, and/or CV death
Timing	At symptom onset
Setting	Outpatient

Appendix 5: Prior Authorization Criteria

Agents for Gout

Goal(s):

- To provide evidenced-based step-therapy for the treatment of acute gout flares, prophylaxis of gout and chronic gout.

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.

Approval Criteria		
2. Will the provider switch to a preferred product? Note: Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics Committee. Preferred products are available without a PA	**Yes:** Inform prescriber of covered alternatives in the class	**No:** Go to #3
3. Is the request for colchicine?	**Yes:** Go to #4	**No:** Go to #7
4. Does the patient have a diagnosis of Behcet's Syndrome with mucocutaneous and/or joint involvement (concomitant NSAID is appropriate)?	**Yes:** Approve for up to 12 months	**No:** Go to #5
5. Does the patient have a cardiovascular diagnosis for which colchicine has demonstrated benefit (e.g., pericarditis, recent myocardial infarction or high cardiovascular disease risk [concomitant NSAID is appropriate])?	**Yes:** Approve for up to 12 months	**No:** Go to #6
6. Does the patient have gout and failed NSAID therapy or have contraindications to NSAIDs or is a candidate for combination therapy, due to failure of monotherapy or initial presentation justifies combination therapy (i.e., multiple joint involvement and severe pain)?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; recommend trial of NSAID
7. Is the request for febuxostat?	**Yes:** Go to #8	**No:** Go to #9
8. Has the patient tried and failed allopurinol or has contraindications to allopurinol?	**Yes:** Approve for up12 months	**No:** Pass to RPh. Deny; recommend trial of allopurinol
9. Is the request for probenecid?	**Yes:** Go to # 10	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
10. Has the patient tried allopurinol and febuxostat or have contraindications to one or both of these treatments?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; recommend a trial of allopurinol or febuxostat
~~11. Is the request for lesinurad?~~	~~**Yes:** Go to #8~~	~~**No:** Pass to RPh. Deny; Medical appropriateness~~
~~12. Is the patient concomitantly taking a xanthine oxidase inhibitor (e.g., allopurinol, febuxostat)?~~	~~**Yes:** Go to #9~~	~~**No:** Pass to RPh. Deny; medical appropriateness~~
~~13. Is the estimated CrCl < 45 mL/min?~~	~~**Yes:** Pass to RPh. Deny; medical appropriateness~~	~~**No:** Approve for 12 months at a maximum daily dose of 200 mg~~

P&T/DUR Review: *12/20 (KS), 1/17 (KS)*
Implementation: *4/1/2017*

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

New Drug Evaluation: Risdiplam (Evrysdi™) oral solution

Date of Review: December 2020
Generic Name: Risdiplam

End Date of Literature Search: 9/30/2020
Brand Name (Manufacturer): Evrysdi™ (Genentech, Inc.)
Dossier Received: yes

Research Questions:

1. What is the efficacy and effectiveness of risdiplam in reducing symptoms, improving functional outcomes and reducing mortality in patients with spinal muscular atrophy (SMA)?
2. What are the harms of risdiplam in patients with SMA?

Conclusions:

- The efficacy of risdiplam was evaluated in two unpublished trials: one double blind, randomized, placebo-controlled trial in children and adults with Type 2 and 3 SMA (SUNFISH) and one open-label trial with historical controls in infants with Type 1 SMA (FIREFISH).[1,2] In SUNFISH, the primary outcome was the mean change from baseline in the total Motor Function Measure 32 (MFM-32) score at Month 12 compared to placebo.[1,2] A statistically significant difference was reported in mean MFM32 score with risdiplam-treated patients compared to placebo (least squares [LS] mean difference: 1.55 (95% CI, 0.30 to 2.81; p-value = 0.016).[1,2] In FIREFISH, the primary outcome was the proportion of infants able to sit without support for at least 5 seconds as measured by item 22 (gross motor skills) of the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) after 12 months post treatment initiation.[1,2] Compared to historical controls, 33% (7/21) of all risdiplam patients and 41% (7/17) of patients given the higher risdiplam dose, were able to sit without support for at least 5 seconds after 12 months of therapy.[1,2]
- There is insufficient evidence to evaluate risdiplam long-term safety or effects on survival, the clinical course of SMA disease, and ventilator dependency.
- In Type 2 and Type 3 SMA patients, risdiplam had increased rates of adverse effects compared to placebo: pyrexia (22% risdiplam vs 17% placebo), diarrhea (17% vs 8%), rash (17% vs 2%), mouth ulcers (7% vs 0%), arthralgia (5% vs 0%), and urinary tract infection (5% vs 0%).[1,2,3] In Type 1 SMA patients, there was increased incidence of upper respiratory tract infection (32%), pyrexia (27%), pneumonia (21%), constipation (16%), diarrhea (13%), vomiting (13%), nasopharyngitis (10%).[1,2,3]
- Trials were unpublished, therefore the quality, risk of bias, applicability, and influence of financial support on the studies were unclear.

Recommendations:

- Add risdiplam to the Preferred Drug List (PDL) class for Spinal Muscular Atrophy agents.
- Implement prior authorization (PA) criteria for risdiplam to ensure appropriate use (**Appendix 2**).
- Designate risdiplam as non-preferred and evaluate comparative costs in executive session.

Author: David Engen, PharmD

Background:
SMA is a heterogeneous autosomal recessive neuromuscular disease characterized by degeneration of motor neurons in the spinal cord which results in progressive weakness, atrophy, and dysfunction of skeletal and respiratory muscles. Severity of disease ranges from progressive infantile paralysis, respiratory failure, and premature death to limited motor neuron loss, ambulation, and normal life expectancy.[4] The incidence of SMA is estimated to range from 1 to 10 individuals per 100,000 live births.[4] Although SMA is rare, it is the leading genetic cause of infantile death due to respiratory insufficiency.[4]

SMA is caused by deletions, rearrangements, or mutations of the survival motor neuron (SMN1) gene on chromosome 5q13 which reduces the overall production of SMN protein.[5] In the human genome, the SMN gene region contains a single SMN1 gene and multiple copies of closely related SMN2 gene.[5,6] Although both genes make SMN protein, a large portion of the SMN2 gene codes for non-functional protein.[5,6] Since SMA patients must rely on the SMN2 pathway to compensate for the loss of SMN1, higher numbers of SMN2 copies tend to positively correlate with functional status.[6] SMA patients with 3 or more copies of SMN2 and a later age of disease onset typically have milder symptoms, are able to ambulate, and have a normal life expectancy.[6] Those with two or fewer SMN2 copies and SMA onset before 6 months of age usually have a poorer prognosis and a median survival of less than 2 years.[6]

There is a wide spectrum of SMA clinical severity, and 5 main subtypes based on age of onset and motor function status. The most common SMA cases are Types 1 through 3 which make up roughly 95% of all cases.[6] SMA Types 0 and 4 are very rare. SMA type 1 is the most frequent (45%) type of SMA and occurs primarily in infants under 6 months of age.[5,6] SMA type 1 infants rarely achieve improvements in motor function or acquire motor developmental milestones.[6] These infants cannot sit unsupported and usually die within the first 2 years of life due to respiratory failure or infection.[5,6] Children with SMA type 2 display muscle weakness that is more conspicuous in the lower extremities. They may sit unassisted but are never able to walk independently. Respiratory failure is not as severe and manifests later in life compared to children with SMA type 1.[6] Children with SMA type 3 develop variable muscle weakness after 18 months of age and are generally able to walk.[5,6] However, as the disease progresses, they may become wheelchair bound.[5,6] Respiratory muscles are rarely affected and life expectancy is normal in type 3 SMA patients.[6] SMA type 4 generally occurs in the second or third decade of life and is the mildest form of the disease characterized by slight muscle weakness and normal life expectancy.[6] The characteristics of each SMA type are described in **Table 1**.

Table 1. SMA classification and characteristics[6]

SMA Type	SMN2 copy numbers	Age of Onset	Motor Function	Median Survival *	Incidence (per 100,000 live births)
0	1	Prenatal	Respiratory failure at birth	Less than 6 months	< 1%
I	2	1 - 6 months	Never able to sit unassisted	<2 years	3.2–7.1 (45% of cases)
II	2-4	7 - 18 months	Able to sit, but unable to independently walk	>2 years (~70% still alive at age 25)	1– 5.3 (20% of cases)
III	3-4	>18 months	Able to independently stand and walk, which may decline with disease progression	Normal	1.5–4.6 (30 % of cases)
IV	4-8	10 - 30 years	Ambulatory	Normal	5% of cases

*Natural history may vary depending on supportive interventions

Diagnosis of SMA is confirmed via genetic testing to assess for homozygous deletions or mutations in the SMN1 gene.[7] Carrier testing is available and carrier frequency is estimated as 1:40 to 1:60.[7] There is no known cure for SMA. Medical care for SMA symptoms typically involves respiratory support, motor function assistance and rehabilitation, as well as optimization of nutritional needs. Swallowing and feeding challenges often result in increased respiratory tract infections, gastrointestinal problems and malnourishment. SMA type 1 patients may require full time noninvasive ventilation greater than 16 hours per day in many cases.[8] Food and Drug Administration (FDA)-approved pharmacotherapy has been developed for the treatment of SMA. Nusinersen targets the modification of the SMN2 gene through the use of antisense oligonucleotides to help produce more functional SMN protein.[9] Other therapies such as onasemnogene abeparvovec have focused on gene-replacement therapy through the use of non-replicating adeno-associated virus (AAV) capsid to deliver fully functional SMN1 gene to motor neurons.[10] Nusinersen must be administered intrathecally every 4 months and onasemnogene abeparvovec is a one-time intravenous infusion.[9,10]

Several scales and tools have been developed to assess functional status in children with SMA. The Motor Function Measure 32 (MFM32) is an ordinal scale used to assess patients with neuromuscular diseases.[2] It is comprised of 32 items to evaluate physical function.[2] Scores are tallied and converted to a 0-100 point scale to be expressed as a percentage of the maximum.[2] A lower score indicates more severe impairment.[2] There is no established minimal clinically important difference between point values on the MFM32.

The Upper Limb Module (ULM) is used in non-ambulatory patients greater than 2 years of age.[11] This assessment was designed to assist in evaluation of young children's ability to perform specific tasks such as lifting small objects, pushing buttons, or using a pencil.[11] It has been validated for use in SMA assessments in a variety of settings. A revised version of the ULM (RULM) was designed to address a wider range of patient cohorts at the extreme ends of the SMA spectrum including ambulatory and non-ambulatory patients.[11] The RULM has 19 scorable items which range from 0 to 2 (0=unable; 1=able, with modification; 2=able, no difficulty) with a maximum possible score of 37.[11]

The Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) is an assessment tool used to measure major clinical development issues in the early childhood years. Although not specific to SMA, the tool measures 5 standardized developmental domains: cognitive, language, motor, social-emotional, and adaptive behavior.[12] The social-emotional and adaptive behavior portions are completed by parental questionnaire while the other 3 areas are administered with child interaction.[12] This tool has not been validated in SMA patients.

The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) was developed by physical therapists to provide a standardized method for motor skill evaluation of neck, trunk, and limb strength of SMA patients. [13] The assessment includes the restricted abilities of SMA patients to sit and roll over and focuses on motor assessment in the prone position. It is a 16-item assessment of functional muscle strength and is scored on a 0–4 scale: no response (0), minimal (1), partial (2), nearly full (3) and complete (4) level of response; with a maximum score of 64 points. It was validated in a small population of children (n = 27) with SMA aged 3 to 260 months (mean age = 49 months).[14] The relationship between CHOP INTEND scores correlated with subject age ($r = -0.51$, $p = 0.007$) and BiPAP utilization ($r = -0.74$, $P < .0001$).[14]

Pediatric neurologists developed the Hammersmith Infant Neurological Exam (HINE) to assist in assessment of neurologic function of infants between 2 and 24 months of age.[15] It includes three sections which measure neurologic signs (section 1), motor function development (section 2), and behavior (section 3). Each section may be assigned a score based on descriptive ratings and tallied. The HINE-section 2 score can be used to evaluate 8 motor milestones in patients with SMA, including voluntary grasp, ability to kick in supine, head control, rolling, sitting, crawling, standing, or walking.[16] A score increase in each category indicates improved function with a minimum score of 0 (inability to perform task) up to a maximum score between 2 to 4 points (full milestone development, depending

upon task).[9] Referenced within the tool are descriptors of each milestone and the age expected to reach based on healthy infants. Although each milestone category varies in value and maximum score, the highest score achievable for HINE-section 2 is 26.

The Hammersmith Functional Motor Scale (HFMS) motor assessment includes upper and lower limb activities as well as head and trunk control.[17] Specific motor functions include rolling, sitting, lifting the head from prone to supine, propping on arms, 4-point kneeling, crawling and standing. Each item is scored on a 3-point scoring system: inability (0), assistance (1), and unaided (2). The total score ranges from 0 (all activities are failed) to 40 (all activities are achieved). Inter-rater reliability was tested on 35 children with an inter-observer agreement greater than 99%.[17] For ambulatory patients with SMA type 3, the HFMS was extended with 13 items to assess walking, running, and jumping which resulted in the HFMSE (HFMS Extended) score.[18] It is scored on a 3-point scale similar to the HFSME, but scores range from 0 to 66.

Spirometry measures Forced Vital Capacity (FVC) which is the volume of air forcibly exhaled from the point of maximal inspiration.[19] FVC has been used to track changes in lung function in SMA type 2 patients.[20] FVC and lung volumes tend to decrease over time in SMA patients and non-invasive ventilation (NIV) support is typically used when FVC is <80% predicted.[20,21] For patients with bulbar dysfunction or with high secretion burden, invasive/tracheostomy ventilation may be necessary due to risk of aspiration.[21] Use of a mask interface for <16 hours per day or nocturnal use is life-sustaining for a number of respiratory and neuromuscular diseases.[21] Patients dependent upon ventilators for life-support usually require a tracheotomy or mask interface for >16 hours per day to prevent life-threatening respiratory complications.[21]

In the past year, approximately 83 patients within the Oregon Health Plan had a SMA-related diagnosis, 22 in the Fee-for-Service (FFS) population and the remaining individuals were enrolled in a coordinated care organization (CCO). The Health Evidence Review Commission (HERC) has included SMA as a funded condition on lines 71, 292, 345, and 377.[22] In addition, SMA carrier screening for pregnant women is addressed in HERC Guideline Note D17.[22] Genetic screening for SMA (CPT 81239) is funded once in a lifetime.[22]

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

Clinical Efficacy:

Risdiplam is a new orally administered small molecule SMN2 splicing modifier designed to promote the inclusion of exon 7 to produce full-length SMN2 mRNA, which results in an increased production of functional SMN protein from the SMN2 gene.[1,2] Risdiplam is indicated for the treatment of SMA in patients 2 months of age and older.[3] Dosing for risdiplam is weight-based and age-dependent given once daily after a meal (see **Appendix 1**). Risdiplam was evaluated by the FDA using data from two unpublished trials: one double blind, randomized, placebo-controlled trial in children and adults with Type 2 and 3 SMA (SUNFISH) and one open-label trial with historical controls in infants with Type 1 SMA (FIREFISH).[1,2] Both studies were unpublished as of September 2020. Details of the study were accessed from the summary report posted on the FDA website.[1,2] Due to its orphan drug status, risdiplam had a Fast Track designation by the FDA.[1,2] Prior to approval, FDA Guidance for Industry was released for the use of historical controls in clinical studies of rare diseases. In the document, the FDA stated that historical controls are appropriate when "(1) there is an unmet medical need; (2) there is a well-documented, highly predictable disease course that can be objectively measured and verified, such as high and temporally predictable mortality; and (3) there is an expected drug effect that is large, self-evident, and temporally closely associated with the intervention."[24] Efficacy was established based on improvements MFM total score compared to placebo, as well as

attainment of motor milestones and survival beyond what would be expected in the normal disease course.[1,2] The FDA noted that efficacy data for the more severe Type 1 SMA patients in the open-label FIREFISH study was originally designated as exploratory.

SUNFISH was multicenter study that consisted of 2 parts.[1,2] Part 1 was a 12-month exploratory dose-finding study in 51 patients with Type 2 and Type 3 (ambulant and non-ambulant) SMA patients.[1,2] Motor and respiratory function findings from the open-label patient assessments were used by an Independent Monitoring Committee to select the dose for part 2.[1,2] Patients from Part 1 were not included in Part 2.[1,2] Part 2 included 180 Type 2 and non-ambulant Type 3 SMA patients.[1,2] Patients were randomized 2:1 to receive a once-daily, weight-based risdiplam oral solution (n=120) or placebo (n=60) for 12 months.[1,2] The primary outcome was the change from baseline in the total MFM32 score at Month 12.[1,2] Relevant secondary endpoints included proportion patients with $\geq$ 3-point change from baseline MFM32 total score at Month 12 with the investigators citing that the medical literature suggests the mean annual decline in untreated patients would be < 1 point per year. Other secondary endpoints assessed at 12 months included change from baseline in mean RULM total score, HFMSE total score, FVC and SMAIS.[1,2] After the 12-month assessment, all placebo patients were switched to risdiplam until month 24.[1,2]

At the time of treatment, there were 71% Type 2 and 29% Type 3 SMA patients, the mean patient age was 9 years (range: 2-25), 51% were female, 67% were white/Caucasian and 19% were Asian.[1,2] Most (87%) of patients were reported to have 3 copies of SMN2, and 67% of patients had scoliosis at screening (10% higher in placebo group).[1,2,23] All patients except one were non-ambulatory.[1,2] Treatment compliance was roughly 98% for placebo and 100% for the risdiplam arm as recorded in a subject diary for all drug administration doses throughout the study at each site.[1,2] There was a statistically significant difference reported in MFM32 score with risdiplam-treated patients compared to placebo (LS mean difference: 1.55 (95% CI, 0.30 to 2.81; p-value = 0.016).[1,2] The clinical importance of a 1.55-point difference on a 100-point scale is unclear. For secondary outcomes, there was a statistically significant difference in proportion patients with $\geq$3-point change from baseline MFM32 score in the risdiplam group compared to placebo (38.3% vs 23.7%, respectively; ARR 14.6%/NNT 7).[1,2] Once again, the clinical significance of even a 3-pont change on a 100-point physical function scale is unclear. A modest but statistically significant difference was also observed in the mean RULM total score for risdiplam compared to placebo patients (mean difference +1.59 points [95% CI, 0.55 to 2.62]; p-value = 0.0469).[1,2] There was not a statistically significant difference between risdiplam and placebo of change from baseline in HFMSE score or FVC measurements.[1,2]

FIREFISH was an open label study in pediatric patients with infantile-onset Type-1 SMA.[1,2] The original protocol had divided the study into 2 parts, Part 1 (12-month, dose finding) and part 2 (motor milestone efficacy and safety at 12 and 24 months).[1,2] A total of 21 subjects were enrolled in Part 1 of the trial each with a confirmed diagnosis of 5q-autosomal recessive SMA with two SMN gene copies or SMA Type 1 symptoms.[2,3] Median patient ages were almost 5 months (range 1 to 7 months) at screening.[1,2] The primary outcome to be measured in part 2 was the proportion of infants able to sit without support for at least 5 seconds as measured by item 22 (gross motor skills) of the BSID-III after 12 months post treatment initiation.[1,2] Assessment was via video recording and centrally reviewed by two independent clinical evaluators.[1,2] The FDA statistical review noted that a statistically significant result would be achieved when a minimum of 6 out of 41 infants are sitting without support for 5 seconds after 12 months of treatment, based on an exact binomial test with a one-sided 5% significance level.[20] Secondary endpoint measures included a mixture of motor assessments (CHOP-INTEND scale), motor milestone achievements (BSID-III and HINE-2 scale), survival and ventilator-free survival, respiratory and feeding assessments, as well as hospitalizations (see Table 3).[1,2] Many of the secondary endpoints were considered exploratory since scales such as CHOP-INTEND and HINE have not been well characterized in the infantile-onset SMA population.[1,2] None of the SMA Type 1 patients were sitting without support at baseline.[1,2] Median baseline scores for the motor assessment tests were as follows: CHOP-INTEND = 24.0, BSID-III = 2.0, HINE-2 = 1.0.[1,2,20] Efficacy was compared to historical controls of motor milestones typically expected for the age group. After the sponsor presented what was considered promising information during Part 1, the FDA allowed the investigators to change protocol.[2] Therefore, Part 1 patients served as the primary intent to treat population for efficacy analysis.[2] Part 2 data were not submitted for FDA review.[2]

Based on only 21 patients observed, results from FIREFISH showed that, compared to historical controls, 33% (7/21) of the risdiplam-treated patients, and 41% (7/17) of patients given the higher dose, were able to sit without support for at least 5 seconds as assessed by Item 22 of the BSID-III gross motor scale after treatment with for 12 months.[1,2] For motor function and developmental milestone secondary endpoints assessed at 12 months via the CHOP-INTEND tool, 52% (11/21) of patients achieved a total score of 40 or higher, 86% (18/21) achieved an increase from baseline of 4 or more points, and 52% (11/21) of patients achieved head control (as defined by score $\geq$3 for item 12).[1,2] HINE-2 12-month assessments also were reported to increase as 43% (9/21) of patients maintained upright head control and 67% (14/21) were considered motor milestone responders.[1,2] There were 91% of patients alive without permanent ventilation at 12 months as well as 86% (18/21) with the ability to feed orally.[1,2] The proportion of patients with no hospitalizations at 12-months was 38% (8/21).[1,2] The FDA noted the potential for observer bias in the open-label study design and recognized that other sources of bias were possible due to the small sample size, lack of concurrent control group, study population differences, and changes in standards of care.[2] Even with the highly predictable clinical course of Type 1 SMA, it was unclear what prognostic variables may have been unidentified in the historical data. Although many of the secondary endpoints in FIREFISH were designed to be assessed at both 12 and 24 months, efficacy data was only submitted for 12 months, so efficacy beyond 12 months is unclear. In addition, FDA statistical reviewers noted that FIREFISH had a multiplicity issue because although Part A was initially designated as exploratory, the sponsor submitted uncontrolled open label data as confirmatory evidence once favorable outcomes were observed.[23] Nonetheless, in the final review, the FDA lead clinical reviewer concluded that the study was rigorously conducted and the study endpoints of sitting unsupported and ventilator-free survival were well-defined with a low potential for bias.[2]

Clinical Safety:
The safety profile for risdiplam is based on observational data in 242 patients from the Phase 2/3 RCT ("SUNFISH") and open label ("FIREFISH") studies in pediatric and adult patients with SMA.[1,2] Also included was supportive safety data obtained from 12 subjects in the open-label phase 2 JEWELFISH study in infantile- and later-onset SMA patients provided to the FDA.[1,2]

In the SUNFISH study, 117/120 patients in the risdiplam group and 59/60 patients in the placebo group completed the study.[1,2] Three patients in the risdiplam group and one patient in the placebo group switched to an alternative treatment (3 - nusinersen and 1 – unspecified). Significant adverse events which lead to dose interruption occurred in 3.3% of patients in both risdiplam and placebo arms.[1,2] Nine patients in the risdiplam group developed a serious pneumonia, with 2 reported as life threatening.[1,2] The most common adverse events in risdiplam-treated patients with an incidence at least 5% greater than placebo was pyrexia (22% risdiplam vs 17% placebo), diarrhea (17% vs 8%), rash (17% vs 2%), mouth ulcers (7% vs 0%), arthralgia (5% vs 0%), and urinary tract infection (5% vs 0%)(see **Table 2**).[1,2,3] There were no reported patient withdrawals due to adverse events.[1,2]

Treatment-emergent adverse events in the FIREFISH study (N=62) that occurred in at least 10% of the patients on risdiplam treatment included upper respiratory tract infection (32%), pyrexia (27%), pneumonia (21%), constipation (16%), diarrhea (13%), vomiting (13%), nasopharyngitis (10%).[1,2] The study recorded 44% of subjects with Grade 3-5 adverse events (Grade 3 = severe; Grade 4 = life threatening; Grade 5= death).[1,2] Most patients (95%) received concomitant medications for an adverse event after risdiplam administration.[1,2,23] Six deaths occurred in the FIREFISH study all due to SMA-related respiratory complications, but the FDA reviewer concluded these were unlikely a cause of risdiplam treatment.[1,2] FDA analysis of TEAEs in the JEWELFISH study were reported to be generally similar to FIREFISH.[1,2] Safety concerns from the non-clinical trials included retinal toxicity as well as epithelial tissue reactions (skin, larynx, eyelid, and gastrointestinal tract), but no such finding was evident in the clinical review.[1,2] FDA reviewers analyzed safety data by demographic subgroups and were unable to find differences in adverse event rates based on age, sex, or race.[1,2] Due to the relatively small number of patients included in the clinical trials and limited duration of exposure, the safety of risdiplam is largely unknown.

Table 2. Adverse Reactions Reported in ≥ 5% of Patients Treated with EVRYSDI and with an Incidence ≥ 5% Greater Than on Placebo in Study 2 Part 2[3]

Adverse Reaction	Risdiplam (N=120) %	Placebo (N=60) %
Fever (pyrexia and hyperpyrexia)	22	17
Diarrhea	17	8
Rash (erythema; maculo-papular, erythematous, or popular rash; dermatitis allergic, and folliculitis)	17	2
Mouth and aphthous ulcers	7	0
Arthralgia	5	0
Urinary tract infection (urinary tract infection and cystitis)	5	0

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Survival
2) Respiratory Support (need for ventilation)
3) Functional improvement (independently sit, stand, walk)
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Motor function improvement from baseline as assessed by the total MFM-32 score at 12 months
2) Proportion of patients with ability to sit unsupported ≥5 seconds at 12 months

Table 3. Pharmacology and Pharmacokinetic Properties.[1-3]

Parameter	
Mechanism of Action	Risdiplam is a survival of motor neuron 2 (SMN2) splicing modifier designed to treat patients with spinal muscular atrophy (SMA) caused by mutations in chromosome 5q that lead to SMN protein deficiency.
Oral Bioavailability	81%; Tmax, oral: 1 to 4 hours
Distribution and Protein Binding	Vd: 6.3 L/kg; Protein binding, albumin: Predominant
Elimination	Renal excretion: 28%, 8% unchanged; Fecal excretion: 53%, 14% unchanged
Half-Life	50 hours
Metabolism	Substrate of flavin monooxygenase 1 and 3 (FMO1 and FMO3); Substrate of CYP1A1, CYP2J2, CYP3A4, and CYP3A7

Abbreviations: CYP=cytochrome-P; L=liters; kg=kilograms; Vd=volume of distribution

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
BP39055[1,2,20] ("SUNFISH") Phase 2/3 DB RCT	1. Risdiplam 5 mg once daily for patients with a BW ≥ 20 kg and 0.25 mg/kg once daily for	Demographics (Part 2): -Mean Age: 10 years -Male/Female: 49%/51% -Race: -White 67% -Asian 19%	ITT: 1. 120 2. 60 Attrition:	Primary Endpoint: Change from baseline in total Motor Function Measure 32 (MFM32) score assessed at 12 months 1. +1.36 points 2. -0.19 points		TEAEs: 1. 93% 2. 92% SAEs 1. 20%	NA for all	Study completed but unpublished so risk of bias and applicability of study unclear.

	patients with a BW <20 kg (part 2 dosing) 2. Placebo Part 1: -Dose finding 12 months (N=51) Part 2: -Efficacy 12 months -Safety 24 months (N=180)	-Black/African American 1% -Multiple 1% -Unknown 12% -Type 2 SMA: 71% -Type 3 SMA: 29% -Patients with 3 copies of SMN2: 87% -scoliosis: 67% -risdiplam: 63% (28% severe) -placebo: 73% (38% severe) <u>Key Inclusion Criteria</u>: - 2 to 25 years of age at screening -Part 1 Type 2 ambulatory and non-ambulatory Type 3 SMA -Part 2 only non-ambulant patients <u>Key Exclusion Criteria</u>: -No current/prior study participation in past 90 days -Concomitant/ previous administration of a SMN2-targeting antisense oligonucleotide, SMN2 splicing modifier -History of gene or cell therapy - Hospitalization for a pulmonary event -Invasive ventilation or tracheostomy -Surgery for scoliosis or hip fixation -Clinically significant abnormalities in laboratory tests -Any major illness within one month before screening	1. 3 (2.5%) 2. 1 (1.7%)	LS mean difference: 1.55 (95% CI, 0.30 to 2.81) p-value = 0.016 <u>Secondary Endpoints</u>: Proportion patients with change from baseline MFM32 total score of 3 or more at month 12 1. 38.3% 2. 23.7% OR 2.35 (95% CI, 1.01 to 5.44) p-value = 0.0469 Mean Revised Upper Limb Module (RULM) score change at Month 12 compared to baseline 1. 1.61 2. 0.02 Mean increase difference 1.59 points (95% CI, 0.55 to 2.62) p-value = 0.0469	NA ARR 14.6 NNT 7 NA	2. 18% <u>AE leading to dose modification or interruption:</u> 1. 7% 2. 3% <u>Most common AEs:</u> -pyrexia 1. 22% 2. 17% -diarrhea 1. 17% 2. 8% -rash 1. 17% 2. 2% -mouth ulcers 1. 7% 2. 0% -arthralgia 1. 5% 2. 0% -urinary tract infection 1. 5% 2. 0%).		
BP39056 [1,2,20] ("FIREFISH") Phase 2/3, multicenter, multinational, open-label, single arm, two-part study	Risdiplam dose: 1. Variable dosing between 0.0106, 0.04, 0.08, 0.2, and 0.25 mg/kg once daily (Cohort 1) 2. 0.2 mg/kg once daily (Cohort 2):	<u>Demographics</u>: -Female: 71% -Caucasian: 81% -Asian: 19% (Median ages and baseline scores reported) -Sx onset: 2 mo. (range 0.9 to 3.0) -screening: 4.9 mo. (range 1.5 to 6.7) -12-month analysis: 16.9 months (range 13.5-18.7 months)	<u>ITT</u>: 1. 4 2. 17 <u>Attrition</u>: 1. 0 2. 0	<u>Primary Endpoint</u>: Proportion of patients sitting without support for > 5 sec (as assessed in Item 22 of the Bayley Scales of Infant and Toddler Development – Third Edition (BSID-III) gross motor scale) at 12 months: 1. (cohort 1): 0 2. (cohort 2): 7 Overall: 7/21 (33%) <u>Secondary Endpoint</u>:	NA for all	<u>Most common AEs - part 1 and 2 data:</u> (N=62) -upper respiratory tract infection (32%) -pyrexia (27%) -pneumonia (21%) -constipation (16%) -diarrhea (13%) -vomiting (13%)	NA for all	Study completed but unpublished so risk of bias and applicability of study unclear.

	Part 1: open-label dose escalation (exploratory) N=21 Part 2: active treatment N=41 (efficacy results for Part 2 not reported)	-No pulmonary care at baseline: 76% -non-invasive BiPAP <16 hrs daily: 14% Baseline scores: -CHOP-INTEND: 24.0 -BSID-III: 2.0 -HINE-2: 1.0 -Able to sit without support: none Country of origin: Italy: 52% France:4% United States: 14% <u>Key Inclusion Criteria</u>: - Age 1-7 months at enrollment -Confirmed diagnosis of 5q-autosomal recessive SMA -two SMN2 gene copies <u>Key Exclusion Criteria</u>: -Same as SUNFISH (sans surgery, abnormal labs) -PLUS- - Non-invasive ventilation or with awake hypoxemia (SaO2 <95%) with or without ventilator support -History of respiratory failure/ severe pneumonia not fully recovered -Recent history (less than <u>6 months</u>) of ophthalmic diseases -Recent therapy of CYP3A4 inhibitor or inducer, OCT-2 or MATE substrate - Presence of non-SMA-related concurrent syndromes or diseases		*Motor Function and Development Milestones* CHOP-INTEND: -score increase of 40 or higher: 1. 1 2. 10 Overall: 11/21 (52%) -increase of 4 or more points from baseline: 1. 3 2. 15 Overall: 18/21 (86%) -achieve head control per score 3 or more on item 12: 1. 2 2. 9 Overall: 11/21 (52%) HINE-2: -head control maintained upright: 1. 0 2. 9 Overall: 9/21 (43%) -motor milestone responders: 1. 1 2. 13 Overall: 14/21 (67%) *Survival and Ventilation-free survival* -Patients alive with or w/o permanent ventilation at month 12: 1. 3 2. 16 Overall: 19/21 (91%) *Respiratory* -Patients not requiring respiratory support at month 12: 1. 1 2. 3 Overall: 4/21 (19%) *Feeding Assessments* -Patients able to feed orally at month 12: 1. 3 2. 15 Overall: 18/21 (86%)		-nasopharyngitis (10%) <u>Deaths:</u> 6 Part 1: 3 Part 2: 3		

				Hospitalizations -Patients with no hospitalizations at month 12: 1. 0 2. 8 Overall: 8/21 (38%)				

Abbreviations [alphabetical order]: ARR = absolute risk reduction; BW = body weight; CGIC = Clinical Global Impression of Change; CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CI = confidence interval; FVC = forced vital capacity; HINE-2 = Hammersmith Infant Neurological Exam 2; HFMS = Hammersmith Functional Motor Scale; ITT = intention to treat; mo = months; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = not significant; PP = per protocol; RCT = randomized controlled trial; SMA = spinal muscular atrophy; SMN = survival motor neuron; Sx = symptom; Tx = treatment; ULM = Upper Limb Module

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Appendix 1: Prescribing Information Highlights

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

EVRYSDI™ (risdiplam) for oral solution
Initial U.S. Approval: 2020

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

EVRYSDI is a survival of motor neuron 2 (SMN2) splicing modifier indicated for the treatment of spinal muscular atrophy (SMA) in patients 2 months of age and older. (1)

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

EVRYSDI must be constituted by a pharmacist prior to dispensing.

Administer orally once daily after a meal using the provided oral syringe. (2.1, 2.4)

Age and Body Weight	Recommended Daily Dosage
2 months to less than 2 years of age	0.2 mg/kg
2 years of age and older weighing less than 20 kg	0.25 mg/kg
2 years of age and older weighing 20 kg or more	5 mg

See Full Prescribing Information for important preparation and administration instructions. (2.1, 2.4)

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

For Oral Solution: 60 mg of risdiplam as a powder for constitution to provide 0.75 mg/mL solution. (3)

---------- **CONTRAINDICATIONS** ----------

None. (4)

---------- **ADVERSE REACTIONS** ----------

The most common adverse reactions in later-onset SMA (incidence at least 10% of patients treated with EVRYSDI and more frequent than control) were fever, diarrhea, and rash. (6.1)

The most common adverse reactions in infantile-onset SMA were similar to those observed in later-onset SMA patients. Additionally, adverse reactions with an incidence of at least 10% were upper respiratory tract infection, pneumonia, constipation, and vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- **DRUG INTERACTIONS** ----------

Avoid coadministration with drugs that are substrates of multidrug and toxin extrusion (MATE) transporters. (7.1)

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

Pregnancy: Based on animal data, may cause fetal harm. (8.1)

Hepatic Impairment: Avoid use in patients with hepatic impairment. (8.6)

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

Revised: 8/2020

Risdiplam

Goal(s):
Approve risdiplam for funded OHP conditions supported by evidence of benefit (e.g. Spinal Muscular Atrophy)

Length of Authorization:
6 months

Requires PA:
- Risdiplam

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:

Age and Body Weight	Recommended Daily Dosage
2 months to less than 2 years of age	0.2 mg/kg
2 years of age and older weighing less than 20 kg	0.25 mg/kg
2 years of age and older weighing 20 kg or more	5 mg

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this a request for continuation of therapy approved by the FFS program?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #3

Approval Criteria		
3. Are the patient's age and the prescribed dose within the limits defined in Table 1?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness. Recommended FDA-approved dosage is determined by age and body weight.
4. Does the patient have a diagnosis of spinal muscular atrophy (SMA), confirmed by SMN1 (chromosome 5q) gene mutation or deletion AND at least 2 copies of the SMN2 gene as documented by genetic testing?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; not funded by the OHP.
5. Is the patient experiencing symptoms of SMA?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness**.**
6. Does the patient have advanced SMA disease (ventilator dependence >16 hours/day or tracheostomy)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #7
7. Has the patient had previous administration of onasemnogene either in a clinical study or as part of medical care?	**Yes:** Pass to RPh. Deny; medical appropriateness**.**	**No:** Go to #8
8. Is the patient on concomitant therapy with a SMN2-targeting antisense oligonucleotide, SMN2 splicing modifier or gene therapy?	**Yes:** Pass to RPh. Deny; medical appropriateness**.**	**No:** Go to #9
9. Is the drug being prescribed by a pediatric neurologist or a provider with experience treating spinal muscular atrophy?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness**.**

Approval Criteria		
10. Is a baseline motor assessment available such as one of the following assessments? • Hammersmith Infant Neurological Examination (HINE-2) • The Motor Function Measure 32 (MFM32) • Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) • Upper Limb Module (ULM) or Revised Upper Limb Module (RULM) • Current status on motor milestones: ability to sit or ambulate	**Yes:** Document baseline results. 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
2. Has the patient shown a positive treatment response in one of the following areas? • Within one month of renewal request, documented improvement from the baseline motor function assessment score with more areas of motor function improved than worsened -OR- • Documentation of clinically meaningful stabilization, delayed progression, or decreased decline in SMA-associated signs and symptoms compared to the predicted natural history trajectory of disease	**Yes:** Approve for additional 6 months.	**No:** Pass to RPh. Deny; medical appropriateness.

Drug Use Research & Management Program
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New Drug Evaluation: cenegermin, ophthalmic solution

Date of Review: December 2020
Generic Name: cenegermin-bkbj

End Date of Literature Search: 09/30/20
Brand Name (Manufacturer): Oxervate™ (Dompé U.S. Inc)

Research Questions:
1. Is there comparative evidence that cenegermin is more effective or safer than current standard of care in the treatment of neurotrophic keratitis?
2. Are there subpopulations of patients for which cenegermin may be more effective or associated with less harm in the treatment of neurotrophic keratitis?

Conclusions:
- There is moderate quality evidence that for patients with stage 2 or 3 neurotrophic keratitis (NK), cenegermin improves corneal healing compared with vehicle at 8 weeks.[1,2]
- There is low quality evidence that cenegermin does not improve corneal sensitivity, vision or quality of life at 8 weeks. There is insufficient evidence to make conclusions about cenegermin's effects on disease progression and deterioration of disease. Long term data is not available to assess these clinical outcomes.
- There is insufficient evidence comparing cenegermin to other treatments commonly used in stage 2 or 3 NK.

Recommendations:
- Make cenegermin non-preferred and apply prior authorization criteria (**Appendix 2**).

Background:
Neurotrophic keratitis (NK) is a rare degenerative corneal disease caused by impairment in the first branch of the trigeminal nerve. The trigeminal nerve provides the cornea with sensation and triggers blinking and tear production in response to stimuli.[3] This sensory innervation protects the cornea from damage. Neurotrophic keratitis causes a reduction in corneal sensitivity which makes the cornea more prone to damage and poor wound healing, which can result in ulcers and perforation.[4] Some causes of NK include herpetic keratitis, intracranial lesions, and neurosurgical procedures that damage the trigeminal nerve.[4] Less common causes include chemical burns, physical injuries, corneal dystrophy, chronic use of topical eye medications (e.g. anesthetics, topical beta blockers, and ketorolac), and systemic conditions such as diabetes mellitus and multiple sclerosis. The estimated prevalence is less than 5 cases per 10,000 persons.[5] There were no previous FDA approved pharmacologic treatments for NK. Those who develop NK rarely report symptoms since there is an absence of corneal sensation, but it can eventually lead to vision loss. Treatment options vary widely and are based on disease severity (**Table 1**). Treatment options are supportive and do not address the underlying cause or improve the speed of healing. The goal of treatment is to slow disease progression, increase corneal sensitivity, and prevent vision loss. Cenegermin is a recombinant human nerve growth factor indicated as an ophthalmic solution for the treatment of NK.[6] The goal is to restore corneal integrity through re-innervation and corneal healing.[3] Due to a lack of long-term data and because it did not meeting cost-effectiveness criteria,

the National Institute for Health and Care Excellence (NICE) did not approve cenegermin for treatment in the United Kingdom.[7] The recommended dose is 6 total drops per day (every 2 hours) for 8 weeks. There are administration and storage requirements that may be challenging. It requires refrigeration by the patient and has a multistep administration procedure involving several components, including one drug vial, one adapter, six pipettes and six disinfectant wipes for one day of therapy.[6]

Table 1: Clinical presentation and treatment options for neurotrophic keratitis

Disease Stage	Clinical Presentation	Standard of Care
Stage 1 (mild disease)	Corneal epithelial changes	Artificial tears, autologous serum eye drops, discontinue toxic topical medications
Stage 2 (moderate disease)	Persistent nonhealing epithelial defects, possible decrease in vision	Therapeutic contact lenses
Stage 3 (severe disease)	Corneal ulceration and stromal involvement, possible pain	Surgical intervention (tarsorrhaphy, amniotic membrane transplantation, conjunctival flap)

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

Clinical Efficacy:

Cenegermin ophthalmic solution (20 mcg/ml dosed 6-times daily) was approved based on two phase II trials that were similar in design (**Table 3**).[1,2] Both were double-masked, vehicle-controlled, randomized controlled trials including patients with stage 2 or 3 (moderate or severe) NK. One study was conducted in Europe[1] and the other in the United States[2]. The most common underlying causes were herpetic eye disease, dry eye disease, ocular surgery, diabetes mellitus and surface injury/inflammation. The most common previous therapies were topical antibacterials and artificial tears.[5] The primary outcome was corneal healing, defined as less than 0.5 mm fluorescein staining in the lesion area at 4 or 8 weeks. However, the FDA requested a post-hoc analysis of a more conservative definition of corneal healing (no residual fluorescein staining and no persistent staining elsewhere in the cornea).[5] After an 8 week double-masked treatment period, patients were eligible for a 24 or 48 week follow-up period.

In both trials, more patients receiving both doses of cenegermin experienced corneal healing compared to those receiving the vehicle control (**Table 3**). This was observed at week 4 and week 8. Complete healing (0 mm in lesion area) was achieved by 49% of patients in the 10 mcg/ml and 58% in the 20 mcg/ml groups compared to 13% in the vehicle group in the study by Bonini et al.[1] The treatment differences were statistically significant compared to vehicle for both doses. A NICE meta-analysis of corneal healing at 8 weeks demonstrated a statistically significant effect with the initial definition (<0.5 mm) (OR 4.24; 95% CI 2.11-8.50; p<0.001) and with the more conservative definition (0 mm in the lesion area) (OR 6.09; 95% CI 2.97-12.50; p<0.001).[7]

There was no significant difference in corneal sensitivity between cenegermin and vehicle in either study, measured using the Cochet-Bonnet esthesiometer.[5] With decreased corneal sensitivity, the blinking and tearing mechanism is reduced, leaving the cornea exposed and prone to damage. There was also no significant difference in vision between treatment and vehicle, as measured by the change from baseline in best-corrected distance visual acuity (BCDVA) score on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart. A post-hoc analysis suggested fewer patients experienced disease progression with cenegermin (22%) compared to vehicle (50%).[2] Follow up to 24 weeks and 48 weeks suggested a high proportion of patients continued to experience corneal healing. However, recurrence rates were more frequent for the cenegermin 10 mcg/ml group (17%) and 20 mcg/ml (20%) compared to the vehicle (10%).[1]

Recurrence is defined as stage 2 or stage 3 NK after complete healing has occurred and the treatment has stopped.[5] In the Pflugfelder et al study, 56.5% of patients in the cenegermin group (20 mcg/ml) compared to 20.8% in the vehicle group achieved complete corneal healing.[2]

There is a lack of evidence comparing cenegermin with any other active comparator other than vehicle. While this was meant to be similar to artificial tears, other clinical interventions are often used in stage 2 and 3 NK. Artificial tears are typically given every 2-4 hours to help improve corneal surface at all disease stages. Additionally, there were no significant differences in vision improvement, corneal sensitivity or quality of life between cenegermin and vehicle. The median baseline lesion size in the study by Plugfelder et al. was 3.1 (95% CI 0.53 to 8.23) in the treatment group compared to 2.99 (95% CI 0.23 to 6.10) in the vehicle group. [2] However, this information was not available in the study by Bonini et al. [1] It remains unknown if treatment with cenegermin will be effective for NK due to all underlying causes or not. Additional limitations include a small number of patients studied, high withdrawal rates, and limited long term follow up data.

Clinical Safety:
Cenegermin has negligible systemic absorption and major systemic side effects are not common and were not different between the groups. There were no serious adverse events or deaths considered to be related to study treatment.[6] Most adverse events in clinical trials were mild and transient. The most common reason for discontinuation due to adverse events was disease progression and reduced visual acuity rather than adverse events related to cenegermin.[5] In total from both studies, there were 38 adverse events (the majority were eye-disorder related) in the vehicle group (50%) and 48 in the approved cenegermin dose (20 mcg/ml) (64%).[5] The adverse events that occurred more frequently in the cenegermin group were cataract, corneal deposits, corneal graft rejection, eye inflammation, eye pain, foreign body sensation, lacrimation increased, ocular hyperemia, visual acuity reduced and intraocular pressure increased.[5]

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Vision loss
2) Disease progression
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Corneal healing (less than 0.5 mm fluorescein staining in the lesion area) at week 4 or 8
2) Completely healed (0—mm lesion staining and no other persistent staining) at week 4 or 8 (post-hoc analysis)

Table 2. Pharmacology and Pharmacokinetic Properties.[6]

Parameter	
Mechanism of Action	Cenegermin is a nerve growth factor involved in the differentiation and maintenance of neurons, which acts through nerve growth factor receptors in the anterior segment of the eye to support corneal innervation and integrity.
Oral Bioavailability	N/A (ophthalmic solution); negligible systemic absorption
Distribution and Protein Binding	N/A (ophthalmic solution); not distributed throughout the body
Elimination	N/A (ophthalmic solution)
Half-Life	N/A (ophthalmic solution)
Metabolism	N/A (ophthalmic solution)

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.Bonini et al.[1] Phase II, DM, MC, PG, RCT	1. Cenegermin 10 ug/ml 6 drops/day 2. Cenegermin 20 ug/ml 6 drops/day 3. Vehicle Control 8 weeks	Demographics: Adults with stage 2 or stage 3 NK • Mean 61 years • 61% female • 91% white • Median lesion size 3.10 mm Key Inclusion Criteria: Stage 2 or 3 NK, Decreased corneal sensitivity BCDVA score of 75 ETDRS letters or fewer, no objective clinical evidence of improvement Key Exclusion Criteria: stage 2 or 3 NK in both eyes, active ocular infection or inflammation, other ocular disease or severe vision loss in the affected eye, history of drug or alcohol abuse	ITT: 1. 52 2. 52 3. 52 PP: 1. 46 2. 40 3. 40 Attrition: 1 .6 (11.5%) 2. 12 (23%) 3. 4 (8%)	Corneal healing at week 4 1. 28 (54.9%) 2. 29 (58%) 3. 10 (19.6%) *Treatment Difference* 1 vs. 3: +35.3%; 97% CI 15.88% to 54.7%; p< 0.001 2 vs. 3: +38.4%; 97% CI 18.96% to 57.83%; p<0.001 Completely healed at week 4 1. 25 (49%) 2. 29 (58%) 3. 7 (13.7%) *Treatment Difference* 1 vs. 3: +35.3%; 97% CI 16.78% to 53.8%; p< 0.001 2 vs. 3: +44.3%; 97% CI 25.8% to 62.75%; p<0.001	ARR 35% / NNT 3 ARR 38% / NNT 3 ARR 35% / NNT 3 ARR 44% / NNT 3	Discontinuation due to AE: 1. 3 (5.8%) 2. 9 (17.3%) 3. 1 (19%) P values not provided	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: unclear; differences in baseline population including underlying cause and prior treatment history. Details of randomization methods not available. Performance Bias: low; patients, investigators and site/sponsor staff were masked to treatment and dosage Detection Bias: low; masked central analysis for efficacy outcome Attrition Bias: unclear; efficacy analyses performed on ITT population with LOCF method, but high and unbalanced rates of attrition Reporting Bias: low; primary outcome requested to be changed by FDA and reported post-hoc Other Bias: high; The trial was supported by Dompe pharmaceuticals, who participated in the design and conduct of the study, data collection, analysis and preparation of the manuscript. All seven authors disclosed financial conflicts with the drug manufacturer. **Applicability**: Patient: Total number of patients studied remains low. Efficacy in patients with stage 1 disease is unknown. Intervention: No dose response identified Comparator: Vehicle was similar to artificial tears, lack of evidence comparing cenegermin with any other comparator often used with artificial tears Outcomes: Commonly used outcome in ocular clinical studies Setting: multicenter in 39 sites in 9 European countries (Belgium, France, Germany, Hungary Italy, Poland, Portugal, Spain and the United Kingdom)

2. Pflugfelder, et al.[2] Phase II, DM, MC, PG, RCT	1. Cenegermin 20 ug/ml 6 drops/day 2. Vehicle Control 8 weeks	Demographics: Adults with stage 2 or stage 3 NK • Mean 65 years • 60% female • 83% white Key Inclusion Criteria: Stage 2 or 3 NK, Decreased corneal sensitivity BCDVA score of 75 ETDRS letters or fewer, no objective clinical evidence of improvement Key Exclusion Criteria: active ocular infection or inflammation, other ocular disease or severe vision loss in the affected eye, history of drug or alcohol abuse	ITT: 1. 24 2. 24 PP: 1. 18 2. 15 Attrition: 1. 6 (25%) 2. 9 (37.5%)	Corneal healing at week 8 1. 15 (62.5%) 2. 6 (25%) *Treatment Difference* +37.5%; 95% CI 11.5% to 63.5%; p< 0.001 Completely healed at week 8 1. 15 (65.2%) 2. 4 (16.7%) *Treatment Difference* +48.6%; 95% CI 24% to 73.1%; p< 0.001	ARR 38% / NNT 3 ARR 48% / NNT 2	Discontinuation due to AE: 1. 4 (17.4%) 2. 3 (12.5%) P values not provided	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: low; appropriate randomization and allocation concealment methods; more stage 3 patients in the treatment group (37.5% vs. 25%) Performance Bias: low; patients, investigators and site/sponsor staff were masked to treatment and dosage Detection Bias: low; masked central analysis for efficacy outcome Attrition Bias: unclear; efficacy analyses performed on ITT population with LOCF method, but high and unbalanced rates of attrition Reporting Bias: low; primary outcome requested to be changed by FDA and reported post-hoc Other Bias: high; The trial was supported by Dompe pharmaceuticals, who participated in the design and conduct of the study, data collection, analysis and preparation of the manuscript. Eight authors disclosed financial conflicts with the drug manufacturer. **Applicability**: Patient: Total number of patients studied remains low Intervention: No dose response identified Comparator: Vehicle and treatment contained the antioxidant methionine as a stabilizer, lack of evidence comparing cenegermin with any other comparator often used in combination with artificial tears Outcomes: Commonly used outcome in ocular clinical studies Setting: multicenter in 11 sites in the United States

Abbreviations [alphabetical order]: AE = adverse events; ARR = absolute risk reduction; BCDVA = best-corrected distance visual acuity; CI = confidence interval; DM = double-masked; ETDRS = early treatment diabetic retinopathy study; ITT = intention to treat; LOCF = last observation carried forward; MC = multicenter; N = number of subjects; NA = not applicable; NK = neurotrophic keratitis; NNH = number needed to harm; NNT = number needed to treat; PG= parallel group; PP = per protocol.

References:

1. Bonini S, Lambiase A, Rama P, et al. Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis. *Ophthalmology.* 2018;125(9):1332-1343.
2. Pflugfelder SC, Massaro-Giordano M, Perez VL, et al. Topical Recombinant Human Nerve Growth Factor (Cenegermin) for Neurotrophic Keratopathy: A Multicenter Randomized Vehicle-Controlled Pivotal Trial. *Ophthalmology.* 2020;127(1):14-26.
3. Deeks ED, Lamb YN. Cenegermin: A Review in Neurotrophic Keratitis. *Drugs.* 2020;80(5):489-494.
4. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol.* 2014;8:571-579.
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6. Oxervate (cenegermin-bkbj) prescribing information. Dompe Inc. October 2019. Availalbe at: https://oxervate.com/wp-content/uploads/2020/05/OXERVATE_Prescribing_Information_102019.pdf.
7. Fleeman N, Mahon J, Nevitt S, et al. Cenegermin for Treating Neurotrophic Keratitis: An Evidence Review Group Perspective of a NICE Single Technology Appraisal. *Pharmacoecon Open.* 2019;3(4):453-461.

Appendix 1: Prescribing Information Highlights

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

OXERVATE™ (cenegermin-bkbj) ophthalmic solution for topical ophthalmic use
Initial U.S. Approval: 2018

----------INDICATIONS AND USAGE----------
OXERVATE is a recombinant human nerve growth factor indicated for the treatment of neurotrophic keratitis. (1)

----------DOSAGE AND ADMINISTRATION----------
One drop of OXERVATE in the affected eye(s), 6 times per day at 2-hour intervals, for eight weeks. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
Ophthalmic solution: cenegermin-bkbj 0.002% (20 mcg/mL) in a multiple-dose vial. (3)

----------CONTRAINDICATIONS----------
None. (4)
----------WARNINGS AND PRECAUTIONS----------
Patients should remove contact lenses before applying OXERVATE and wait 15 minutes after instillation of the dose before reinsertion. (5.1)

----------ADVERSE REACTIONS----------
The most common adverse reactions (incidence >5%) are eye pain, ocular hyperemia, eye inflammation and increased lacrimation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Dompé U.S. Inc. at 1-833-366-7387 or FDA at 1-800-FDA-1088 or www.fda.gov./medwatch.

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

Revised: 8/2018

Cenegermin-bkbj (Oxervate™)

Goal(s):
- Ensure medically appropriate use of cenegermin

Length of Authorization:
8 weeks

Requires PA:
- Cenegermin-bkbj (Oxervate™)

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this a request for continuation of therapy?	**Yes**: Pass to RPh. Deny; medical appropriateness Cenegermin is only approved for 8 weeks of therapy	**No:** Go to #3
3. Is this for the treatment of Stage 2 or 3 neurotrophic keratitis?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is it prescribed by or in consultation with an ophthalmologist?	**Yes:** Approve for 8 weeks	**No:** Pass to RPh. Deny; medical appropriateness

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Policy Proposal: Drug Discontinuation Safety Net

Purpose of the Proposal:
Identify patients with gaps in therapy for maintenance medications and offer patient case management services to identify reasons for gaps in care, provide patient education, and connect patients with appropriate resources.

Background:
The current COVID-19 pandemic has changed how many people receive medical care in Oregon. Provider offices may be closed, operating with limited staffing, or have limited office hours. Some providers may be prioritizing urgent or emergency services or only providing remote or virtual services, and patients may be hesitant to schedule routine office visits during the pandemic. Because of these changes, some patients may be unable to see a provider or unable to get to the pharmacy to have their prescription filled in a timely manner. Many pharmacies have begun offering mail delivery or drive-through services to accommodate patient needs. However, with so many changes, there is potential for gaps in care where patients may be unable to fill their routine prescriptions.

In order to support prescription needs for FFS members during the current pandemic, a pilot program was created to provide patient outreach and case management for members with discontinuation of a high-risk medication. High-risk medications were defined based on medication type and patient diagnoses (see methods below), and referrals were prioritized based on case manager availability and medication importance. The program was intended to ensure members were able to fill essential prescriptions particularly when they may be unable to physically pick up their prescription or when their provider office may have been closed. Case managers can help ensure that members have adequate access to essential medications by connecting patients with additional resources, assisting in care coordination, communicating with provider offices, and providing patient education.

While this initiative was started to provide patient support during the current pandemic, many factors can cause barriers to care and delay access to necessary medications. In particular, care coordination can often be improved during transitions of care. The FFS population has a significant number of patients transitioning to and from coordinated care organizations (CCOs). Because CCOs are location-based, if patients move locations or loose Medicaid coverage, they may be disenrolled from their current CCO and re-enrolled in a different CCO. Because members are typically eligible for FFS coverage before CCO enrollment occurs, FFS serves as a safety net to provide Medicaid coverage when members are first enrolled or moving between CCOs. Ensuring access to essential maintenance medications for patients with transitional FFS coverage can improve care for Medicaid members. Similarly, delays in obtaining appropriate medications can arise from other system-wide issues. The following are just a few examples of scenarios that have the potential to cause delays in therapy:

- Changes in a patient's primary care provider
- Referrals to a specialist
- Drug shortages
- Changes in claims edits or Medicaid drug coverage
- Changes in other insurance policies
- Prior authorizations which are not submitted in a timely manner or are lacking necessary information for approval

Patient outreach may be able to mitigate some of these issues by identifying the reason for the delay in therapy, providing patient education, and supporting care coordination.

Methods:
Patients were targeted for outreach if they had previously filled more than 84 days of a routine maintenance medication and had a recent gap in therapy of more than 14 days (**Appendix 1**). Patients were excluded if they were deceased, not currently enrolled in FFS, enrolled in Medicare, or had other primary insurance. Patients were also excluded if they had a more recent paid claim for medication in the same PDL class, indicating a switch to a different therapy. Patients were prioritized for case management referral based on patient and medication characteristics. Types of referrals have included the following categories:

- Insulin in patients with a diagnosis of type 1 diabetes
- Anticoagulants, statins, or antihypertensive medications in patients with established cardiovascular disease
- Antiepileptics in patients with a seizure disorder
- Maintenance asthma or COPD inhalers
- HIV medications
- Medications for opioid use disorder

Patients were identified weekly and information on the patient, medication history, prescribing provider, and most recent pharmacy were sent to case managers who called patients to offer support and case management services if needed (**Appendix 2**). There are several inherent limitation with using claims data to identify gaps in therapy. For example, patients may have paid cash for a prescription, had a recent hospitalization, or have an excess supply of medication on hand from previous prescriptions. Insurance coverage or Medicaid enrollment may change resulting in missing or delayed claims data. Changes in directions or dose may result in inaccurate days' supply on billed claims. These limitations may result in inaccurate identification of patients. Additionally, enrollment with case management services is voluntary and members can opt out of receiving calls from the case management program. However, providing the opportunity for patient education and support for patients with an actual gap in therapy has the potential to improve adherence and prevent utilization of emergency services and hospitalizations.

Planned assessments to evaluate impact of this policy include evaluation for re-initiation of therapy after referral, medication adherence before and after referral, and utilization of emergency services.

Discussion and Preliminary Results:
In total, 90 patients were referred for case management outreach in the first 5 weeks of the pilot program. Because this is a recently initiated pilot program, outcomes are not yet available for all patients. Outcomes for initial outreach have been documented for 52 patients. Of these patients, case management services were able to contact 36 patients (69%). Nineteen patients (37%) were enrolled in a partial case management program. Patients in the partial case management program decline to be actively enrolled with a case manager, but agree to receive quarterly health-related newsletters and reminders for healthy activities such as flu shots. Three patients (6%) were enrolled in full case management services for a chronic condition (smoking cessation, diabetes, and asthma/COPD). With full enrollment in case management services, patients are matched with a case manager who performs an initial assessment to identify medication issues, gaps in care, social determinants of health, and patient needs. Based on this initial assessment, case managers work to connect the patient with community resources, communicate with their providers and pharmacies, and provide education regarding their medications, non-pharmacological treatments, and diagnoses.

Even though claims data indicated that many patients may have a gap in therapy, most patients identified still had an adequate supply of their medication or were about to refill the medication. However, some patients were identified who may not have been taking their medications routinely or may have missed doses. In a few cases, gaps in care, changes in insurance coverage, or individual patient circumstances resulted in delayed access to routine medications. For these patients, case management outreach can help provide patient education regarding importance of medication adherence, assist in coordination with provider offices, and provide resources in order to connect members with adequate services to enhance care and avoid adverse events. Outreach to members can also increase awareness of case management services and provide an additional resource if members encounter issues or wish to be engaged in the future.

Recommendations:

- Implement a case management referral program for patients with gaps in therapy for high-risk maintenance medications.

Appendix 1: RetroDUR Inclusion and Exclusion Criteria

Inclusion Criteria

- Patients previously on stable therapy, defined as patients with >=84 days and <=180 supply for a drug in past 150 days AND
- Recent >2 week gap in therapy in the prior month for a "high-risk drug" in the drug categories below. Gap in therapy was defined as 2 weeks of no covered days for the drug.
    - Anticoagulants
    - Platelet Inhibitors
    - HIV
    - Diabetes, Insulins
    - Antipsychotics (exclude drugs which are typically prescribed for sleep)
    - Antidepressants (exclude drugs which are typically prescribed for sleep)
    - Benzodiazepines
    - Substance Use Disorders, Opioid and Alcohol
    - Immunosuppressants
    - Maintenance asthma/COPD inhalers (anticholinergic, long-acting beta-agonist, corticosteroid, and combination inhalers)
    - Antiepileptics in patients with a seizure disorder in past 2 years (ICD-10 G40x)
    - Blood pressure medications (ACE inhibitors, ARBs, beta-blockers, diuretics) in patients with cardiovascular disease
    - Statins in patients with cardiovascular disease

Exclusion criteria

- Patients who are:
    - Deceased
    - Enrolled in a CCO
    - Enrolled in Medicare OR
    - Have other primary insurance
- Patients with a more recent paid claim for the same drug or a paid claim for a different drug in the same PDL class (indicating therapy was switched)
- Patients previously identified and referred to case management in the past 3 months

Appendix 2: Patient, Drug and Problem Solving Information Collected for Case Management

Patient Information:

- Patient ID
- Patient Name
- Patient phone number
- Number and list of conditions which may increase risk for COVID-related complications (e.g. age, diabetes, pulmonary diagnoses, chronic kidney disease, liver disease, immunosuppression, etc)

Drug Information:

- PDL Class of identified drug with a gap in therapy
- Generic drug name
- Drug strength
- Total days' supply in last 6 months
- Med possession ratio (MPR) in the past 6 months
- Last filled date
- Last fill days' supply
- Duration of gap in therapy

Potential problem-solving issues:

- Recent denied claims for the drug indicating a pharmacy tried to fill a prescription
- PA submission needed based on error codes associated with denied claims
- Issues with prescriber enrollment based on error codes associated with denied claims
- Possible new prescription needed based on the prescription number, refill number, and total days' supply
- Potential drug shortage based on the FDA drug shortage list

Appendix 3: Outcome Information for the RetroDUR Report

Case Management Referrals

- Number of patients referred
- Number of patients with subsequent paid claim within 1 month of referral for the identified drug
- Number of patients with subsequent paid claim within 1 month of referral for a different drug in the same PDL class
- Patients with an improvement of ≥10% in med possession ratio (MPR) in the 3 months after referral (compared to MPR in 3 months before referral) for identified drug (HSN)

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Policy Evaluation: Expert Consultation for Long-term Antipsychotics in Children

Research Questions:

- What proportion of prescribers referred for expert consultation completed a consultation with the Oregon Psychiatric Access Line about Kids (OPAL-K)?
- How many patients had a change in psychiatric therapy after referral for prescriber consultation?
- Were there any differences in provider type or patients (e.g., medication therapy or demographics) who had a consult compared to those that did not?

Conclusions:

- This preliminary analysis identified 77 patients with at least 6 months of use of a newly initiated antipsychotic who were referred to OPAL-K for peer-to-peer provider consultation from August to December 2019. Forty-four percent of prescribers successfully scheduled and completed a consultation for their patients.
- Of the patients referred for consultation, 80% had more than 2 antipsychotics prescribed within a 60 day period, 84% lacked an appropriate diagnosis based on claims data, and 62% did not have documented glucose monitoring. Approximately 50% of patients were prescribed antipsychotics from a non-specialist prescriber. The most commonly prescribed antipsychotics were risperidone and aripiprazole.
- Forty-four percent of patients (n=34) had no change in drug therapy or monitoring in the 3 months following consultation with a mental health specialist. In the 3 months following referral for consultation, 26% of patients (n=20) had a decrease in dose of their antipsychotic, and 19% (n=15) had a gap in therapy of more than 45 days indicating their antipsychotic may have been discontinued. Thirteen patients (17%) had new metabolic monitoring following referral for consultation. Changes in therapy were similar for those that scheduled a consultation compared to those who were only sent a letter. However, the small population size makes it difficult to discern differences between groups.
- Pediatric physicians were the most commonly referred prescribers, followed by mental health nurse practitioners and psychiatrists. Overall differences in providers or patient characteristics were small upon comparison of those with consultation with those who were unable to schedule a consultation. The analysis was limited by the small number of patients identified for each group.

Recommendations:

- Continue to monitor drug therapy changes after referral and consultation in pediatric patients on long-term antipsychotics.

Background:

There is limited evidence on the use of antipsychotics in children. Many antipsychotics are not FDA-approved for young children and many guidelines recommend extreme caution when prescribing antipsychotics to young children. In addition, long-term use of antipsychotics can be associated with complications including increased risk for metabolic syndrome, diabetes, and movement disorders. Long-term use of antipsychotics is often recommended only in combination with non-pharmacological therapy, and only when benefit has been established.

In order to improve care and promote medically appropriate use for young children on antipsychotics, this initiative targeted new-start patients less than 10 years of age who were initiating long-term antipsychotic therapy, defined as at least 6 months of covered days in the past 9 months. Patients were prioritized for referral based on relevant risk factors, including patients lacking relevant psychiatric diagnoses or glucose monitoring based on claims data or patients prescribed antipsychotics from a non-specialist. Mental health specialists were included in the program if their patient had other relevant risk factors. Two separate interventions were conducted as part of this process. First, a fax was sent to the prescribing provider notifying them that their patient had been identified based on long-term antipsychotic use. The fax included information on why their patient was being referred, and the prescribing provider was instructed to contact OPAL-K for a consultation on their patient in order to promote the best care for their patient. If providers did not call for a consultation, OPAL-K staff reached out to the provider to schedule a consultation. Consultation as part of this program is not required, and providers were allowed to refuse the offer for consultation. In some cases, patients may have changed providers and the current provider responsible for ongoing therapy was unable to be identified based on claim data or unable to be reached to schedule a consultation.

Methods:

This is a preliminary pre- and post-analysis to evaluate antipsychotic utilization in the 3 months before and after the referral date for each member. Both first- and second-generation antipsychotics were included in the analysis and were identified based on PDL class. Patients were included if a profile was sent to OPAL-K as part of this initiative. Patients were excluded if they had less than 60 days of Medicaid enrollment in the 3 months following referral for consultation.

Baseline characteristics including age, ethnicity, and relevant risk factors were identified at the time of the referral. Relevant psychiatric diagnoses were evaluated based on ICD-10 codes associated with medical claims the 1 year before the referral. Typically ICD-10 codes were categorized according to the first 3 characters. Prescriber type was based on primary provider taxonomy. Medication flags identified at the time of the referral are documented in **Table 1**. Patients were stratified based on completion of a consultation with OPAL-K experts from August to December 2019.

Changes in drug therapy were compared for the 3 months before and after referral to OPAL-K. The following definitions were used to evaluate therapy:

- Drug discontinuation was defined as a break in therapy of at least 45 days.
- Switches in antipsychotic therapy were assessed based on the unique molecular entity (HSN code; **Table A1**).
- Glucose monitoring was defined using the codes in **Table A3**.
- Utilization of other psychotropic medications was classified by the number of unique molecular entities (HSNs). The analysis included any products in the psychiatric system. Oral antipsychotics were defined according to PDL class: first-generation antipsychotics and second-generation antipsychotics.
- Concurrent use of more than one oral antipsychotic or other psychotropic was defined as at least 60 days of therapy with no more than a 2-week gap in coverage.
- Average dose per day was evaluated in the 3 months before and after the OPAL-K referral. Changes in drug dose were categorized according to the relative decrease or increase per day. Relative percent change was calculated based on difference in the average dose for the before and after groups over 3 months divided by the average dose in the before group.
- Outpatient medical visits were identified using codes in **Table A4**. All provider NPIs associated with these medical visits were evaluated to determine if the prescriber of the antipsychotic was involved in the visit.

Results:

Table 1 shows baseline demographics for patients referred to OPAL-K for expert consultation. Most patients referred were White and over 5 years of age. Patients were referred for expert consultation based on several criteria including duration of antipsychotic use, lack of metabolic monitoring, lack of FDA-approved diagnosis, use of more than 2 antipsychotics, and lack of mental health specialist prescribing. Eighty percent of referred patients had more than 2 antipsychotics prescribed within a 60 day period, 84% lacked an appropriate diagnosis based on claims data, and 62% did not have documented glucose monitoring. The most commonly prescribed antipsychotics were risperidone and aripiprazole. Approximately 50% of patients were prescribed antipsychotics from a non-specialist prescriber. Overall, 77 patients were identified, and 44% of prescribers successfully completed a consultation for their patients. Two groups were available for comparison: 1) patients whose provider had received a fax and completed a consultation AND 2) patients whose provider had received a fax but did not complete a consultation. Demographics were similar between patients who completed a consultation and those only notified via fax, though compared to patients whose provider did complete a consultation, patients without consultation were slightly more likely to be prescribed multiple antipsychotics (86% vs. 73.5%) and not have an FDA-approved diagnosis based on claims data (88.4% vs. 79.4%).

Table 2 describes the most common mental health diagnoses identified in children referred for consultation. The most common identified diagnoses were ADHD, severe stress and adjustment disorders (including PTSD), conduct disorders, and anxiety disorders. The majority of patients had more than one mental health diagnosis. For example, patients with a diagnosis of ADHD often had other mental health diagnoses such as mood or developmental disorders identified based on the patient's medical claims. Providers who did not have a consultation were slightly more likely to prescribe antipsychotics in patients with diagnoses of severe stress and adjustment disorders, conduct disorders and anxiety disorders compared to providers who did complete an expert consultation. Provider types identified for referral for peer-to-peer consultation are described in **Table 3**. Pediatric physicians were the most commonly referred prescribers, followed by mental health nurse practitioners and psychiatrists. When categorizing providers by prescriber type, there were slight differences in the proportion of providers who were able to complete a consultation compared to those unable to complete a consultation, but any conclusions are significantly limited by the small population size.

Changes in drug therapy are described in **Tables 4 and 5** for patients whose providers completed a consultation and providers without a consultation. While numbers of patients are small, screening for metabolic disorders was increased in both populations after referral for consultation. In the 3 months following referral for consultation, 26% of patients (n=20) had a decrease in dose of their antipsychotic, and 19% (n=15) had a gap in therapy of more than 45 days indicating their antipsychotic may have been discontinued (**Table 4**). Six patients were switched to a different antipsychotic, most commonly risperidone to aripiprazole (**Table 5**). There were only slight changes in numbers of other concurrently psychotropic medications, and numbers are too small to discern any reliable patterns (data not shown). In the 3 months following provider notification and outreach for a consultation, subsequent medical visits were slightly more common for providers who completed a peer-to-peer consultation (58.8%) compared to those without a consultation (46.5%). With a longer duration of follow-up more changes in therapy may be documented.

Table 1. Baseline Demographics of Patients Referred to OPAL-K.

	All Patients	
	77	%
Age		
0-5	9	11.7%
6-9	68	88.3%
Race		
White	47	61.0%
Unknown	24	31.2%
Other	6	7.8%
Criteria for Referral*		
No diabetes screen within the past year	48	62.3%
≥2 antipsychotics prescribed within prior 60 days	62	80.5%
Non-psychiatrist prescriber	38	49.4%
No diagnosis of schizophrenia, bipolar, or autism	65	84.4%
Antipsychotics prescribed in the 6 months before referral*		
1 risperidone	57	74.0%
2 aripiprazole	24	31.2%
3 olanzapine	2	2.6%
4 paliperidone	1	1.3%
5 asenapine maleate	1	1.3%
6 chlorpromazine HCl	1	1.3%
Patients with a medical visit with their prescribing provider in the 3 months following OPAL-K referral	40	51.9%

*Patients may be counted more than once if they meet multiple criteria or were prescribed multiple medications

Table 2. Common Diagnoses Identified in Children Referred to OPAL-K. Patients may be counted more than once if they have multiple diagnoses.

		All Patients		Patients w/consultation		Patients w/o consultation	
		77	%	34	44%	43	56%
Top 10 psychiatric diagnosis (categorized by the first 3 characters of the ICD-10 code)							
1	F90 - Attention-deficit hyperactivity disorders	51	66.2%	22	64.7%	29	67.4%
2	F43 - Reaction to severe stress, and adjustment disorders	34	44.2%	13	38.2%	21	48.8%
3	F91 - Conduct disorders	30	39.0%	11	32.4%	19	44.2%
4	F41 - Other anxiety disorders	28	36.4%	9	26.5%	19	44.2%
5	F88 - Other disorders of psychological development	18	23.4%	11	32.4%	7	16.3%
6	F34 - Persistent mood [affective] disorders	16	20.8%	8	23.5%	8	18.6%
7	F84 - Pervasive developmental disorders (including autistic disorder)	11	14.3%	6	17.6%	5	11.6%
8	F80 - Specific developmental disorders of speech and language	11	14.3%	7	20.6%	4	9.3%
9	F93 - Emotional disorders with onset specific to childhood	10	13.0%	6	17.6%	4	9.3%
10	F32 - Major depressive disorder, single episode	6	7.8%	2	5.9%	4	9.3%

Table 3. Prescriber characteristics based on primary provider taxonomy for the most recent antipsychotic claim before the referral.

	All Patients		Patients w/consultation		Patients w/o consultation	
Provider Type	77	%	34	44%	43	56%
PHYSICIAN-PEDIATRICS	21	27.3%	9	26.5%	12	27.9%
NURSE PRACTITIONER - PSYCHIATRIC/MENTAL HEALTH	20	26.0%	12	35.3%	8	18.6%
PHYSICIAN-PSYCHIATRY&NEUROLOGY-PSYCHIATRY	10	13.0%	4	11.8%	6	14.0%
PHYSICIAN-PSYCHIATRY&NEUROLGY-CHILD&ADOLESCENT PSYCHIATRY	9	11.7%	2	5.9%	7	16.3%
NURSE PRACTITIONER - PEDIATRICS: PEDIATRICS	5	6.5%	2	5.9%	3	7.0%
NURSE PRACTITIONER - FAMILY	4	5.2%	0	0.0%	4	9.3%
PHYSICIAN-PEDIATRICS-DEVELOPMENTAL BEHAVORIAL PEDIATRICS	2	2.6%	2	5.9%	0	0.0%
PHYSICIAN-FAMILY MEDICINE	2	2.6%	1	2.9%	1	2.3%
PHYSICIAN-PEDIATRICS-ADOLESCENT MEDICINE	1	1.3%	1	2.9%	0	0.0%
STUDENT IN AN ORGANIZED HEALTH CARE EDUCATION/TRAINING PROGRAM	1	1.3%	1	2.9%	0	0.0%
CLINICAL NURSE SPECIALIST - PSYCHIATRIC/MENTAL HEALTH	1	1.3%	0	0.0%	1	2.3%
DENTIST	1	1.3%	0	0.0%	1	2.3%

Table 4. Changes in drug utilization in the 3 months following OPAL-K referral compared to the 3 month before referral.

	All Patients		Patients w/consultation		Patients w/o consultation	
	77	%	34	44%	43	56%
No change in drug therapy or monitoring (patients not meeting any of the criteria below)	34	44.2%	14	41.2%	20	46.5%
Antipsychotic drug discontinuation	15	19.5%	7	20.6%	8	18.6%
Discontinuation of other psychotropic drug	5	6.5%	3	8.8%	2	4.7%
Change to a different antipsychotic	6	7.8%	3	8.8%	3	7.0%
New glucose monitoring	13	16.9%	7	20.6%	6	14.0%
Change in Average Daily Dose						
No change or less than 25% change in dose	43	55.8%	18	52.9%	25	58.1%
Decrease of >=25%	20	26.0%	9	26.5%	11	25.6%
Increase of >=25%	14	18.2%	7	20.6%	7	16.3%

Table 5. Changes in antipsychotic therapy assessed in the 3 months following OPAL-K referral

	Drug prescribed before referral	Drug prescribed after referral
Patient 1	aripiprazole	haloperidol
Patient 2	risperidone	ziprasidone
Patient 3	risperidone	aripiprazole
Patient 4	risperidone	aripiprazole
Patient 5	risperidone	aripiprazole
Patient 6	risperidone	aripiprazole

Limitations:

- This is a before/after analysis and does not control for potential confounding factors (of which there are many). Other characteristics may influence which prescribers contact OPAL-K for a consult (e.g., number of patients seen, familiarity with OPAL services, time available in the day, availability of administrative office staff, prior consults with specialists, or previous provider education or experience with antipsychotics). Similarly, there are many factors which can influence medication therapy including new diagnoses, disease severity, adverse events, involvement of parents/guardians in care, frequency of follow-up, or availability of providers for medical visits.

- This analysis did not include a comparison to a similar patient population with no intervention (educational fax or consultation). The fax intervention notifying providers of the need for expert consultation includes patient specific information on why they are being contacted (e.g., long-term antipsychotic use, lack of metabolic monitoring, etc). It is possible that the fax intervention itself may result in changes in prescribing or glucose monitoring.
- This analysis assesses only short-term changes in therapy within the 3 months following referral for consultation. The long-term impact of consultation and referral for peer-to-peer consultation is unknown at this time.
- The count of patients with follow-up medical visits may be inaccurate as billing provider for medical visit may not match prescribing provider even if prescriber was involved in care for that visit. Codes identified are the most common codes associated with routine medical visits, but all types of medical visits may not be captured.
- Prescriber type may not be accurate and may not reflect all specialties. Prescribers may change over time.
- Diagnoses is identified via medical claims and may not accurately reflect the diagnosis for the identified antipsychotic prescription.
- Dose changes were evaluated based on an average days' supply for paid claims and may not accurately reflect what the patient is actually taking.
- Blood glucose screening was identified based on medical claims. Patients may have access to glucose screening via other mechanisms which would not be identified via claims data.
- The small number of patients in this analysis significantly limtis ability to identify changes in prescribing between groups.

Appendix 1. Drug Coding Information
Table A1. Antipsychotics

Class	HSN	Generic
Antipsychotics, 1st Gen	001621	chlorpromazine HCl
Antipsychotics, 1st Gen	001626	fluphenazine HCl
Antipsychotics, 1st Gen	001662	haloperidol
Antipsychotics, 1st Gen	001661	haloperidol lactate
Antipsychotics, 1st Gen	039886	loxapine
Antipsychotics, 1st Gen	001664	loxapine succinate
Antipsychotics, 1st Gen	001627	perphenazine
Antipsychotics, 1st Gen	001637	pimozide
Antipsychotics, 1st Gen	001631	thioridazine HCl
Antipsychotics, 1st Gen	001668	thiothixene
Antipsychotics, 1st Gen	001667	thiothixene HCl
Antipsychotics, 1st Gen	001630	trifluoperazine HCl
Antipsychotics, 2nd Gen	024551	aripiprazole
Antipsychotics, 2nd Gen	046175	asenapine
Antipsychotics, 2nd Gen	036576	asenapine maleate
Antipsychotics, 2nd Gen	042283	brexpiprazole
Antipsychotics, 2nd Gen	042552	cariprazine HCl
Antipsychotics, 2nd Gen	004834	clozapine
Antipsychotics, 2nd Gen	046280	lumateperone tosylate
Antipsychotics, 2nd Gen	037321	lurasidone HCl
Antipsychotics, 2nd Gen	011814	olanzapine
Antipsychotics, 2nd Gen	034343	paliperidone
Antipsychotics, 2nd Gen	043373	pimavanserin tartrate
Antipsychotics, 2nd Gen	014015	quetiapine fumarate
Antipsychotics, 2nd Gen	008721	risperidone
Antipsychotics, 2nd Gen	021974	ziprasidone HCl

Table A2. Drug dosing for unique antipsychotic dosage forms

Class	Generic	GSN	Route	FormDesc	TextDrugStr	Strength
Antipsychotics, 2nd Gen	cariprazine HCl	075566	PO	CAP DS PK	1.5 mg (1)-3 mg (6)	3
Antipsychotics, 2nd Gen	clozapine	064429	PO	ORAL SUSP	50 mg/mL	50
Antipsychotics, 2nd Gen	asenapine	080406	TD	PATCH TD24	3.8 mg/24 hour	3.8
Antipsychotics, 2nd Gen	asenapine	080407	TD	PATCH TD24	5.7 mg/24 hour	5.7
Antipsychotics, 2nd Gen	asenapine	080408	TD	PATCH TD24	7.6 mg/24 hour	7.6
Antipsychotics, 2nd Gen	aripiprazole	058594	PO	SOLUTION	1 mg/mL	1
Antipsychotics, 2nd Gen	risperidone	026177	PO	SOLUTION	1 mg/mL	1
Antipsychotics, 2nd Gen	risperidone	071304	PO	SYRINGE	1 mg/mL	1
Antipsychotics, 2nd Gen	risperidone	071305	PO	SYRINGE	2 mg/2 mL	1
Antipsychotics, 2nd Gen	risperidone	071306	PO	SYRINGE	3 mg/3 mL	1
Antipsychotics, 2nd Gen	quetiapine fumarate	074076	PO	TAB24HDSPK	50 mg (3)-200 mg (1)-300 mg (11)	300
Antipsychotics, 1st Gen	fluphenazine HCl	003821	PO	ELIXIR	2.5 mg/5 mL	0.5
Antipsychotics, 1st Gen	chlorpromazine HCl	003794	PO	ORAL CONC	100 mg/mL	100
Antipsychotics, 1st Gen	chlorpromazine HCl	003795	PO	ORAL CONC	30 mg/mL	30
Antipsychotics, 1st Gen	fluphenazine HCl	003822	PO	ORAL CONC	5 mg/mL	5
Antipsychotics, 1st Gen	haloperidol lactate	003971	PO	ORAL CONC	2 mg/mL	2
Antipsychotics, 1st Gen	thioridazine HCl	003857	PO	ORAL CONC	100 mg/mL	100
Antipsychotics, 1st Gen	thioridazine HCl	003858	PO	ORAL CONC	30 mg/mL	30
Antipsychotics, 1st Gen	thiothixene HCl	003994	PO	ORAL CONC	5 mg/mL	5

Table A3. Codes associated with glucose monitoring

CPT Code	Description
80047	basic metabolic panel w/calcium, ionized
80048	basic metabolic panel w/calcium, total
80050	general health panel
80053	comprehensive metabolic panel
80065	metabolic panel
80069	renal function panel
82947	glucose assay
82948	reagent strip/blood glucose
82950	glucose test

82951	glucose tolerance test
82952	glucose tolerance test –added samples
82953	glucose tolerance test
82961	glucose tolerance test, IV
82962	glucose test (home use)
83036	A1c
83037	A1c home use
D0411	Hba1c in-office point of service testing
81506	endocrinology (T2DM), biochemical assays of seven analytes

Table A4. Codes associated with medical visits

CPT Code	Description
90791	Psychiatric Diagnostic Evaluation
90792	Psychiatric Diagnostic Evaluation With Medical Services
90832	Psychotherapy, 30 Minutes
90833	Psychotherapy, 30 Minutes
90834	Psychotherapy, 45 Minutes
90836	Psychotherapy, 45 Minutes
90837	Psychotherapy, 60 Minutes
90839	Psychotherapy For Crisis, First 60 Minutes
90840	Psychotherapy For Crisis
90846	Family Psychotherapy, 50 Minutes
90847	Family Psychotherapy Including Patient, 50 Minutes
90849	Multiple-Family Group Psychotherapy
90853	Group Psychotherapy
90882	Environmental Intervention For Management Of Medical Conditions
90887	Explanation Of Psychiatric, Medical Examinations, Procedures, And Data To Other Than Patient
96110	Developmental Screening
96112	Developmental Test Administration By Qualified Health Care Professional With Interpretation And Repo
96113	Developmental Test Administration By Qualified Health Care Professional With Interpretation And Repo
96127	Brief Emotional Or Behavioral Assessment
96130	Psychological Testing Evaluation By Qualified Health Care Professional, First 60 Minutes
96131	Psychological Testing Evaluation By Qualified Health Care Professional, Additional 60 Minutes
96132	Neuropsychological Testing Evaluation By Qualified Health Care Professional, First 60 Minutes

96133	Neuropsychological Testing Evaluation By Qualified Health Care Professional, Additional 60 Minutes
96136	Psychological Or Neuropsychological Test Administration And Scoring By Qualified Health Care Profess
96137	Psychological Or Neuropsychological Test Administration And Scoring By Qualified Health Care Profess
96138	Psychological Or Neuropsychological Test Administration And Scoring By Technician, First 30 Minutes
96150	Health And Behavior Assessment Each 15 Minutes
96151	Health And Behavior Re-Assessment Each 15 Minutes
96152	Health And Behavior Intervention, Individual Each 15 Minutes
96154	Health And Behavior Intervention, Family And Patient Each 15 Minutes
97151	Behavior Identification Assessment By Qualified Health Care Professional, Each 15 Minutes
97153	Adaptive Behavior Treatment By Protocol, Administered By Technician Under Direction Of Qualified Hea
97155	Adaptive Behavior Treatment With Protocol Modification Administered By Qualified Health Care Profess
97156	Family Adaptive Behavior Treatment Guidance By Qualified Health Care Professional (With Or Without P
97157	Family Adaptive Behavior Treatment Guidance By Qualified Health Care Professional Without Patient Pr
97530	Therapeutic Activities To Improve Function, With One-On-One Contact Between Patient And Provider, Ea
98966	Telephone Assessment And Management Service, 5-10 Minutes Of Medical Discussion
98967	Telephone Assessment And Management Service, 11-20 Minutes Of Medical Discussion
99201	New Patient Office Or Other Outpatient Visit, Typically 10 Minutes
99202	New Patient Office Or Other Outpatient Visit, Typically 20 Minutes
99203	New Patient Office Or Other Outpatient Visit, Typically 30 Minutes
99204	New Patient Office Or Other Outpatient Visit, Typically 45 Minutes
99205	New Patient Office Or Other Outpatient Visit, Typically 60 Minutes
99211	Established Patient Office Or Other Outpatient Visit, Typically 5 Minutes
99212	Established Patient Office Or Other Outpatient Visit, Typically 10 Minutes
99213	Established Patient Office Or Other Outpatient Visit, Typically 15 Minutes
99214	Established Patient Office Or Other Outpatient, Visit Typically 25 Minutes
99215	Established Patient Office Or Other Outpatient, Visit Typically 40 Minutes
99215	Established Patient Office Or Other Outpatient, Visit Typically 40 Minutes
99354	Prolonged Office Or Other Outpatient Service First Hour
99383	Initial New Patient Preventive Medicine Evaluation, Age 5 Through 11 Years
99392	Established Patient Periodic Preventive Medicine Examination, Age 1 Through 4 Years
99393	Established Patient Periodic Preventive Medicine Examination, Age 5 Through 11 Years
99403	Preventive Medicine Counseling, Approximately 45 Minutes
99404	Preventive Medicine Counseling, Approximately 60 Minutes
99441	Physician Telephone Patient Service, 5-10 Minutes Of Medical Discussion
99442	Physician Telephone Patient Service, 11-20 Minutes Of Medical Discussion

99443	Physician Telephone Patient Service, 21-30 Minutes Of Medical Discussion
99492	Initial Psychiatric Collaborative Care Management, First 70 Minutes In The First Calendar Month
99493	Subsequent Psychiatric Collaborative Care Management, First 60 Minutes In Subsequent Month Of Behavi
G0463	Hospital Outpatient Clinic Visit For Assessment And Management Of A Patient
H0002	Behavioral Health Screening To Determine Eligibility For Admission To Treatment Program
H0004	Behavioral Health Counseling And Therapy, Per 15 Minutes
H0017	Behavioral Health; Residential (Hospital Residential Treatment Program), Without Room And Board, Per
H0019	Behavioral Health; Long-Term Residential (Non-Medical, Non-Acute Care In A Residential Treatment Pro
H0031	Mental Health Assessment, By Non-Physician
H0032	Mental Health Service Plan Development By Non-Physician
H0034	Medication Training And Support, Per 15 Minutes
H0036	Community Psychiatric Supportive Treatment, Face-To-Face, Per 15 Minutes
H0037	Community Psychiatric Supportive Treatment Program, Per Diem
H0039	Assertive Community Treatment, Face-To-Face, Per 15 Minutes
H2000	Comprehensive Multidisciplinary Evaluation
H2011	Crisis Intervention Service, Per 15 Minutes
H2012	Behavioral Health Day Treatment, Per Hour
H2013	Psychiatric Health Facility Service, Per Diem
H2014	Skills Training And Development, Per 15 Minutes
H2027	Psychoeducational Service, Per 15 Minutes
T1016	Case Management, Each 15 Minutes
T1017	Targeted Case Management, Each 15 Minutes
T1024	Evaluation And Treatment By An Integrated, Specialty Team Contracted To Provide Coordinated Care To
T1040	Medicaid Certified Community Behavioral Health Clinic Services, Per Diem
T2022	Case Management, Per Month
T2023	Targeted Case Management; Per Month