Drug Use Research & Management Program
OHA Division of Medical Assistance Programs
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Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, September 27, 2018 1:00 - 5:00 PM
HP Conference Room
4070 27th Ct. SE
Salem, OR 97302
MEETING AGENDA

NOTE: Any agenda items discussed by the DUR/P&T Committee may result in changes to utilization control recommendations to the OHA. Timing, sequence and inclusion of agenda items presented to the Committee may change at the discretion of the OHA, P&T Committee and staff. The DUR/P&T Committee functions as the Rules Advisory Committee to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 as required by 414.325(9).

	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	T. Klein (Chair)
	D. Department Update	T. Douglass (OHA)
	E. Legislative Update	T. Douglass (OHA)
1:10 PM	II. CONSENT AGENDA TOPICS	T. Klein (Chair)
	A. Overactive Bladder DERP Summary	
	B. Oral and Parenteral Antipsychotics Literature Scan	
	C. Pancreatic Enzymes Literature Scan	
	1. Public Comment	
	III. PREFERRED DRUG LIST NEW BUSINESS	
1:15 PM	A. Pulmonary Hypertension Class Update	S. Servid (OSU)
	1. Class Update/Prior Authorization Criteria	
	2. Public Comment	
	3. Discussion of Clinical Recommendations to OHA	
1:30 PM	B. Attention Deficit Hyperactivity Disorder Literature Scan	J. Page (OSU)
	1. Literature Scan/Prior Authorization Criteria	
	2. Public Comment	
	3. Discussion of Clinical Recommendations to OHA	
1:45 PM	C. Vaginal Antibiotics Drug Class Review	K. Sentena (OSU)
	1. Class Review	
	2. Public Comment	
	3. Discussion of Clinical Recommendations to OHA	

2:05 PM	D. Aimovig® (erenumab-aooe) New Drug Evaluation 1. New Drug Evaluation/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	D. Engen (OSU)
2:20 PM	E. Palynziq™ (pegvaliase-pqpz) New Drug Evaluation 1. New Drug Evaluation/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	J. Page (OSU)
2:35 PM	F. Hepatitis C Direct Acting Antivirals Class Update 1. Class Update/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	M. Herink (OSU)
3:10 PM	BREAK	
	IV. DUR NEW BUSINESS	
3:20 PM	A. Benzodiazepine Policy Evaluation and DERP Report 1. DERP Report/Prior Authorization Criteria 2. Policy Evaluation 3. Public Comment 4. Discussion of Clinical Recommendations to OHA	S. Servid (OSU)
	V. DUR OLD BUSINESS	
3:50 PM	A. Cystic Fibrosis 1. Follow-Up from July P&T/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	M. Herink (OSU)
4:00 PM	B. Botulinum Toxins Prior Authorization Update 1. Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	J. Page (OSU)
4:05 PM	VI. EXECUTIVE SESSION	
4:50 PM	VII. RECONVENE for PUBLIC RECOMMENDATIONS	
	VIII. ADJOURN	

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Oregon Pharmacy and Therapeutics Committee – Appointed members

Name	Title	Profession	Location	Term Expiration
William Origer, M.D.	Physician	Residency Faculty	Albany	December 2020
Caryn Mickelson, Pharm.D.	Pharmacist	Pharmacy Director	Coos Bay	December 2020
Tracy Klein, Ph.D., F.N.P.	Public	Nurse Practitioner	Portland	December 2020
James Slater, Pharm.D.	Pharmacist	Pharmacy Director	Beaverton	December 2020
Kelley Burnett, D.O.	Physician	Pediatric Medical Director	Grants Pass	December 2019
Dave Pass, M.D.	Physician	Medical Director	West Linn	December 2019
Stacy Ramirez, Pharm.D.	Pharmacist	Community Pharmacist	Corvallis	December 2019
Cathy Zehrung, R.Ph.	Pharmacist	Pharmacy Manager	Silverton	December 2018
Phil Levine, Ph.D.	Public	Retired	Lake Oswego	December 2018
Rich Clark, M.D., M.P.H.	Physician	Anesthesiologist	Salem	December 2018
Walter Hardin, D.O., M.B.A.	Physician	Medical Director	Hillsboro	December 2018

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, July 26, 2018, 1:00-5:00 PM
DXC Building
Salem, OR 97301

MEETING MINUTES

NOTE: Any agenda items discussed by the DUR/P&T Committee may result in changes to utilization control recommendations to the OHA. Timing, sequence and inclusion of agenda items presented to the Committee may change at the discretion of the OHA, P&T Committee and staff. The DUR/P&T Committee functions as the Rules Advisory Committee to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 as required by 414.325(9).

Members Present: Tracy Klein, PhD, FNP; Phil Levine, PhD; Walter Hardin, DO, MBA; Jim Slater, PharmD; Caryn Mickelson, PharmD; Stacy Ramirez, PharmD; Cathy Zehrung, RPh; Kelley Burnett, DO; William Origer, MD

Members Present by Phone:

Staff Present: Richard Holsapple, RPh; Roger Citron, RPh; Trevor Douglass, DC, MPH; Sarah Servid, PharmD; Lindsay Newton; Dee Weston; Renae Wentz, MD; Julia Page, PharmD; Jonnaliz Corbett; Deanna Moretz, PharmD; Megan Herink, PharmD; David Engen, PharmD; Amanda Parish

Staff Present by Phone: Kathy Sentena, PharmD

Audience: Rick Frees, Vertex; Greg Rasmussen, Vertex; *Lisa Allen, Vertex; Bobbi Jo Drum, BMS; Stephanie Lattig, NovoNordisk; *Anthony Hoovier, NovoNordisk; Andrew Tschernia, OSU; Mike Moore, Otsuka; Aaron Fitzcharles, Pacific University; Dan Allen, Sanofi Genzyme; Mike Ketcher, Sanofi Genzyme; Julie Brown, Harmony Biosciences; *Mae Kwong, Janssen; Van Ann, Vu; Katie Peters, Salud Medical Center; Tim McFerron, Alkermes; Kelly Wright, Lupin Pharma; *Anthony Wheeler, Lilly; Venus Holder, Lilly; Nancy Yuguna, Lilly; Laura Jeffcoat, Abbvie; Anthony Mckenzie, OSU; Sierra Carpenter, OSU; Amy Burns, AllCare; Danielle Shannon, WVP Health Authority; *Kara Shirley, Care Oregon/MHCAG; *Amy Garee; *Forrest Bell; *Marilyn Hartell; Sheila Stidal Collari; John Goddard, GSK

(*) Provided verbal testimony

Written testimony provided: Forrest Bell

I. CALL TO ORDER

A. The meeting was called to order at approximately 1:04 pm. Introductions were made by Committee members and staff. No new conflict of interests were declared.
B. Dr. Douglass provided a department update and legislative update.

ACTION: Motion to approve, 2nd, All in Favor.

II. CONSENT AGENDA TOPICS

A. Approval of agenda and May minutes presented by Mr. Citron. (pages 4-7)

ACTION: Motion to approve, 2nd, All in Favor.

B. P&T Methods
C. CMS Annual Report
D. P&T Annual Report
E. Quarterly Utilization Reports

ACTION: Motion to approve, 2nd, All in Favor.

III. DUR ACTIVITIES

A. ProDUR Report (pages 8-16)
B. RetroDUR Report (pages 17-23)
C. Oregon State Drug Reviews (pages 24-25)
    1. A Review of Implications of FDA Expedited Approval Pathways, Including the Breakthrough Therapy Designation

ACTION: Motion to approve, 2nd, All in Favor.

IV. PREFERRED DRUG LIST NEW BUSINESS

A. Oral Cystic Fibrosis Modulators Class Update (pages 26-51)
Dr. Herink presented the class update and recommended:

    1. Continue to require PA for approval in appropriate patients. No changes to the PDL. Remove the requirement of an FDA-approved CF gene mutation test from PA criteria.

ACTION: The Committee amended the proposed PA criteria to remove question #21 (case management) and instead document in the criteria an acknowledgement that if therapy is approved, a referral will be made to case management; remove question #13 (FEV1 restriction); and modify question #17 to correlate with the FDA-approved mutations for tezacaftor/ivacaftor. Motion to approve, 2nd. All in favor. Approved.

B. Newer Diabetes Class Update (pages 52-100)
Dr. Sentena presented the class update and recommended:

1. No changes to the PDL based on efficacy and safety data. Add new formulations to existing PA criteria.
2. Evaluate comparative costs in executive session.

ACTION: The Committee amended the proposed PA criteria to remove amylin analog (sub-item 5) from question #6 in SGLT-2 PA criteria. Motion to approve, 2nd. All in favor. Approved.

C. Asthma Biologics DERP Summary (pages 101-124)
Dr. Moretz presented the class update and recommended:

1. No changes to the PDL based on evidence.
2. Add benralizumab to PA criteria for monoclonal antibodies for asthma.
3. Revise PA criteria to include expanded indication for mepolizumab in patients experiencing eosinophilic granulomatosis with polyangiitis (EGPA).
4. Evaluate comparative costs in executive session.

ACTION: The Committee amended the proposed PA criteria to add a new question around co-prescribing auto-injectable epinephrine; require at least one hospitalization or 2 ED visits in the past 12 months while receiving a maximally dosed inhaled corticosteroid AND 2 additional controller drugs; modify question #4 to go to #10 if answered "yes"; and change wording from "another" monoclonal antibody to "newly approved" monoclonal antibody in question #4. Motion to approve, 2nd. All in favor. Approved.

D. Radicava® (edaravone) New Drug Evaluation (pages 125-137)
Dr. Engen presented the drug evaluation and recommended:

1. Implement PA criteria for edaravone.

ACTION: The Committee amended the proposed PA criteria to remove the age requirement in question #2; remove question #5; move #4 (asking if continuation) to after #1; modify renewal criteria question #2 to say "prescriber" and add questions identical to #8 and #9 to the renewal criteria. Motion to approve, 2nd. All in favor. Approved.

E. Neuropathic Pain DERP Summary (pages 138-163)
Dr. Moretz presented the drug evaluation and recommended:

1. No further review or research needed at this time.
2. Maintain pregabalin extended-release tablets as non-preferred on the PMPDP.
3. Apply clinical PA criteria to pregabalin extended-release tablets.
4. Evaluate comparative costs in executive session.

ACTION: Motion to approve, 2nd. All in favor. Approved.

V. DUR OLD BUSINESS

A. Sedatives (pages 164-167)

Dr. Page presented the proposed updates to the Sedatives PA criteria with the following recommendation:

1. Update PA criteria to clarify FDA-recommended initial and maximum daily dose recommendations as well as use in palliative care settings.

ACTION: The Committee amended the proposed PA criteria to modify the approval duration for palliative care to lifetime. Motion to approve, 2nd. All in favor. Approved.

B. New Drug Policy (pages 168-170)
Dr. Servid presented the proposed updates to the New Drug Policy PA criteria with the following recommendation:

1. Modify PA criteria.

ACTION: Motion to approve, 2nd. Majority in favor, one opposed. Approved. The Committee asked that the policy be brought back for additional information on how this may be able to be applied to oncology.

VI. EXECUTIVE SESSION

Present in room: Tracy Klein, PhD, FNP; Phil Levine, PhD; Walter Hardin, DO, MBA; Jim Slater, PharmD; Caryn Mickelson, PharmD; Stacy Ramirez, PharmD; Cathy Zehrung, RPh; Kelley Burnett, DO; William Origer, MD; Richard Holsapple, RPh; Roger Citron, RPh; Trevor Douglass, DC, MPH; Sarah Servid, PharmD; Lindsay Newton; Dee Weston; Renae Wentz, MD; Julia Page, PharmD; Jonnaliz Corbett; Deanna Moretz, PharmD; Megan Herink, PharmD; David Engen, PharmD; Amanda Parish; Anthony McKenzie; Sierra Carpenter; Katie Peters, Aaron Fitzcharles; Andrew Tschernia

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VII. RECONVENE FOR PUBLIC RECOMMENDATIONS * After executive session

A. Newer Diabetes Class Update (pages 52-100)
*__ACTION:__ No changes to the PMPDP.
Motion, 2nd, All in Favor. Approved.
B. Asthma Biologics DERP Summary (pages 101-124)
*__ACTION:__ No changes to the PMPDP.
Motion, 2nd, All in Favor. Approved.
C. Neuropathic Pain DERP Summary (pages 138-163)
*__ACTION:__ No changes to the PMPDP.
Motion, 2nd, All in Favor. Approved.

VIII. ADJOURN

Drug Use Research & Management Program
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OHSU Drug Effectiveness Review Project Summary Report – Drugs to Treat Overactive Bladder

Date of Review: September 2018

Date of Last Review: May 2015
Literature Search: 03/01/2018

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

Research Questions:
1. How do drugs used to treat overactive bladder (OAB) compare in efficacy and effectiveness?
2. How do drugs used to treat OAB compare in safety and harms?
3. Are there subgroups of patients in whom effectiveness or harms of drugs used to treat OAB differ? Subgroups of interest are demographics (age, racial groups, gender), socioeconomic status, other medications (drug-drug interactions), comorbidities (drug-disease interactions), and pregnancy.

Conclusions:
- High quality evidence from 4 randomized controlled trials (RCTs) comparing mirabegron to solifenacin found no difference at 12 weeks for reducing incontinence episodes per 24 hours.[1] Moderate quality evidence due to small numbers of events found no difference in adverse event withdrawals.[1] Moderate quality evidence showed urgency episodes were reduced more with mirabegron than solifenacin, but the difference was small (2 RCTs, 0.54 fewer episodes per 24 hours, 95% confidence interval [CI] -0.92 to -0.16).[1]
- Mirabegron was compared to tolterodine extended release (ER) in 5 RCTs which provided moderate to high quality evidence of comparative efficacy.[1] At 8-12 weeks, incontinence episodes were reduced more with mirabegron than tolterodine, but the difference was very small (5 RCTs, 0.15 fewer episodes per 24 hours, 95% CI -0.27 to -0.04).[1] No differences were found in urgency episodes between mirabegron and tolterodine ER. Tolterodine had a higher incidence of dry mouth (8-13% with tolterodine versus 3-4% with mirabegron), but there were no significant differences in adverse event (AE) withdrawals.[1]
- Three small, fair quality RCTs assessed different head to head comparisons for OAB medications. One fair-quality trial (n=119) compared fesoterodine with solifenacin.[2] Significant differences in efficacy were not identified between fesoterodine and solifenacin in this trial. However, significantly more patients receiving fesoterodine withdrew from the study due to AEs compared to solifenacin (10% vs. 0%; p=0.013).[1] Another small, fair-quality trial (n=60) compared darifenacin with trospium over 4 weeks.[3] Measures of urinary frequency, urgency, nocturia, and urge urinary incontinence improved in both groups; however, no statistically significant differences in these outcomes were observed at 2 or 4 week assessments.[1] No serious adverse events (SAEs) or withdrawals due to AEs were noted with darifenacin or trospium ER in this small trial.[1] An additional fair-quality RCT (n=132) comparing solifenacin to oxybutynin immediate release (IR) found fewer patients taking solifenacin withdrew due to adverse events compared to oxybutynin (13% vs. 30%, relative risk [RR] 0.45, 95% CI 0.23 to 0.91).[4] Of the specific adverse events of interest, only the difference in number of participants who experienced dry mouth was significant; solifenacin 5 mg (35.29%) versus oxybutynin IR 15 mg (82.81%) [RR0.43, 95% CI 0.30 to 0.60].[1] The evidence from these 3 trials is insufficient to draw conclusions, primarily due to the small sample size and the lack of corroborating evidence for each head-to-head comparison.[1]

- One good quality retrospective cohort study conducted using the Taiwan National Health Insurance Research Database enrolled patients with diabetes and sought to determine the risk for dementia associated with use of solifenacin, tolterodine, and oxybutynin.[5] The assessment from this study concluded risk for dementia in patients with diabetes was significantly increased with solifenacin, tolterodine and oxybutynin.[5] The adjusted hazard ratios were: solifenacin HR 2.16, 95% CI 1.81 to 2.58; tolterodine HR 2.24, 95% CI 1.85 to 2.73; and oxybutynin HR 2.35, 95% CI 1.96 to 2.81.[1] This study did not control for actual duration of drug exposure and did not formally compare the drugs with each other.[1]

Recommendations:

- There is no significant new comparative evidence from the 2018 Drug Effectiveness Review Project (DERP) report to support differences in efficacy or serious harms between the OAB drugs.
- No further review or research needed at this time. Review comparative drug costs in the executive session.

Summary of Prior Reviews and Current Policy

Previous Oregon Pharmacy and Therapeutics Committee reviews found no evidence to support differences in efficacy or harms between OAB drugs. The preferred and non-preferred status of the OAB medications on the Preferred Drug List (PDL) are presented in **Appendix 1**. Utilization is guided by PDL status as no PA criteria have been implemented for this class of medications. Preferred OAB medications include fesoterodine and oxybutynin. Almost all of the Oregon Medicaid Fee-For-Service utilization for this class of drugs is for oxybutynin (97%).

Methods:

The June 2018 drug class update on drugs to treat OAB by the Drug Effectiveness Review Project at the Pacific Northwest Evidence-based Practice Center at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class.

The original report is available to Oregon Pharmacy and Therapeutics Committee members upon request. An executive summary report is publically available in the agenda packet and on the DURM website.

The purpose of the DERP reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. DERP reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. OHSU does not recommend or endorse any guideline or recommendation developed by users of these reports.

Summary Findings:

Eighteen head-to-head trials and 1 observational cohort study are new in this DERP update of the OAB summary review published in 2013. The majority of the RCTs were 8 to 12 weeks in duration, with 1 RCT being 52 weeks.[1] Most of the studies were funded by drug manufacturers. There have not been any new therapeutic agents added to this medication class since 2012. The drugs approved to treat overactive bladder symptoms are outlined in **Table 1.** New comparative evidence was identified for mirabegron, fesoterodine, darifenacin, trospium, tolterodine, oxybutynin, and solifenacin.[1]

Table 1: Drugs Used to Treat Overactive Bladder[1]

Generic Name	Trade Name	Dosage Form/Route	FDA Approval
Mirabegron	Myrbetriq®	Extended-release oral tablet	6/28/2012
Fesoterodine fumarate	Toviaz®	Extended-release oral tablet	10/31/2008
Darifenacin	Enablex®	Extended-release oral tablet	12/22/2004
Solifenacin succinate	Vesicare®	Oral tablet	11/19/2004
Trospium chloride	Generic	Oral tablet Extended-release oral capsule	5/28/2004
Oxybutynin transdermal system	Oxytrol® Gelnique®	Extended-release transdermal film Transdermal gel	2/26/2003 1/27/2009
Tolterodine tartrate	Detrol® Detrol® LA	Oral tablet Extended-release oral capsule	3/25/1998
Oxybutynin chloride	Generic	Oral tablet Extended-release oral tablet	7/16/1975
Flavoxate hydrochloride	Generic	Oral tablet	1/15/1970

The effectiveness outcomes evaluated in the recent randomized controlled trials (RCTs) included the following metrics reported over 24 hours: change in mean number of incontinence episodes; change in mean number of urgency episodes; change in mean number of pads used; and patient symptoms assessments. The harms outcomes included withdrawals due to AEs, SAEs, and specific adverse events associated with anticholinergic medications (constipation, dry mouth, cognitive changes, blurred vision, and cardiac abnormalities).

Head to Head Comparisons

Mirabegron versus Solifenacin

Six RCTs compared mirabegron with solifenacin. Two of these were rated poor quality for multiple reasons, including poor or unclear reporting, imbalance between groups at baseline, and high attrition rates.[1] The remaining 4 studies were of moderate to high quality.[1] The studies were 12 weeks in duration, included 67% to 100% females, and less than 25% of subjects were non-White.[1] Sample sizes ranged from 80 to 1,887 patients and all trials included the most commonly used doses; mirabegron 50 mg per day and solifenacin 5 mg per day.[1] Three RCTs reported the mean change in incontinence episodes per 24 hours.[6-8] For the comparison of mirabegron 50 mg per day versus solifenacin 5 mg per day, there was not a statistically significant difference in incontinence episodes from baseline to 12 weeks (3 RCTs, n=2741, mean difference [MD] -0.061 episodes per 24 hours, 95% CI -0.189 to 0.067).[1] Differences between other doses (mirabegron 25 mg per day, solifenacin 2.5 and 10 mg per day) were also not significant.[1] Confidence in these findings is high; future studies are very unlikely to change them.[1]

Only 2 RCTs measured and reported urgency episodes in a way that could be compared directly between the monotherapy groups.[6,9] Pooling the results of these studies, mirabegron 50 mg per day results in a significantly greater reduction than solifenacin 5 mg per day (mean difference in change from baseline of -0.54 episodes per 24 hours; 95% CI -0.92 to -0.16).[1] Confidence in these findings is moderate due to some inconsistency in the magnitude of the findings; future studies could change the findings.[1] Only 2 trials reported measures of patient assessment of changes in symptoms in a way that could be compared or

combined.[6,9] These 2 RCTs reported changes in the Patient Perception of Bladder Condition scale (6 items, change scores range from -2 to 2 with negative scores indicating improvement), although a clinically meaningful difference between groups has not been established.[1]

Withdrawals due to adverse events were reported in all 4 RCTs, and the pooled DERP assessment shows no difference between groups (5% versus 5%; RR 0.94, 95% CI 0.53 to 1.68).[1] Confidence in these findings is moderate due to small numbers of events.[1] SAEs were reported in 3 RCTs, with less than 2% incidence per group; no differences were observed between mirabegron and solifenacin.[6-8] The pooled DERP relative risk estimate of SAE incidence is 1.15 (95% CI 0.80 to 2.21).[1] Specific adverse events described in the mirabegron versus solifenacin trials included cardiac arrhythmias, falls/syncope, dry mouth and blurred vision. Differences in the frequency of AEs were not apparent, except that a somewhat higher incidence of dry mouth was reported with solifenacin (7.7%) compared to mirabegron (3.8%).[1] Statistical significance was not reported for this outcome.

Mirabegron versus Tolterodine ER

Six comparative RCTs of mirabegron versus tolterodine met inclusion criteria for the DERP update. The percent of female enrollment ranged from 67 to 82% of participants; over 80% of subjects were White in 3 trials, while race was not reported in the other 3 trials.[1] Sample sizes ranged from 749 to 2,444 patients. Five of the RCTs used tolterodine ER 4 mg per day, while one only reported using tolterodine 4 mg once per day without specifying whether the IR or ER formulation was used.[10] Mirabegron dosing ranged from 25 mg to 200 mg per day, with the most common doses being 50 mg and 100 mg per day.[1] Most of the studies were 8 to 12 weeks long, although one study was conducted over 12 months.[1] Pooling data from 5 trials reporting incontinence at 8 to 12 weeks finds that mirabegron 50 mg reduces the number of episodes significantly more than tolterodine ER 4 mg (mean difference in change from baseline -0.15 episodes per 24 hours, 95% CI -0.27 to -0.04).[1] Although this difference is very small, the DERP authors reported high confidence in this finding.[1] Pooling the 4 studies that reported the change in urgency episodes, the difference favors mirabegron but is very small and does not reach statistical significance. (-0.12, 95% CI -0.23 to 0.00; P = 0.052).[1] Confidence in these findings is high; future studies are very unlikely to change them.[1]

Pooling results from 6 RCTs finds no difference between mirabegron 50 mg and tolterodine ER 4 mg daily in the proportions of patients withdrawing due to adverse events (4.7% versus 4.9%, RR 0.97, 95% CI 0.76 to 1.25, I^2 = 0%).[1] Confidence in these findings is moderate, and future studies may alter these results.[1] Rates of serious adverse events were low, with no differences between groups.[1] Across 5 RCTs, the rate of constipation did not differ between mirabegron 50 mg per day and tolterodine ER 4 mg per day at 8 to 12 weeks or at 12 months.[1] Constipation rates were low, around 2%.[1] In 3 short-term trials, spontaneous reporting of dry mouth was more than twice as frequent with tolterodine than with mirabegron (8-13% of patients reporting dry mouth with tolterodine vs. 3-4% with mirabegron).[1]

Fesoterodine versus Solifenacin

One recently published fair-quality trial (n=119) compared fesoterodine with solifenacin.[2] The mean age was 59 years and all participants were female. The primary outcome was change in the 15 point OAB Symptom Scale (OABSS) which sums the score of 4 symptoms (daytime frequency, nighttime frequency, urgency and urgency incontinence).[11] Higher scores on the OABSS scale indicate more severe symptoms. Over 12 weeks, both fesoterodine 4 mg and solifenacin 5 mg significantly reduced OABSS scores (-9.4 vs. -8.2), but the difference between the drugs was not significant.[1] Significantly more patients receiving fesoterodine withdrew from the study due to adverse events compared to solifenacin (10% vs. 0%; p=0.013).[1] More patients receiving fesoterodine compared to solifenacin experienced constipation (5% vs. 2%) and dry mouth (14% vs. 5%); although the differences were not significant (p=0.26 and p=0.19, respectively).[1] This evidence is insufficient to draw conclusions, primarily due to the small sample size and the lack of corroborating evidence.[1]

Trospium versus Darifenacin

One fair-quality trial (n=60) compared darifenacin 7.5 mg with trospium ER 60 mg.[3] The mean age of participants was 64 years, 23% were female, and all subjects were of Asian ethnicity. Over 4 weeks, both groups showed significant improvement in OABSS scores, though the difference between the groups was not significant.[1] Scale scores of urinary frequency, urgency, nocturia, and urge urinary incontinence improved with both darifenacin and trospium, although no significant differences were observed between the groups at 2 and 4 week assessments.[1] There were no serious adverse events or withdrawals due to adverse events, and there was no significant difference in the mean increase in the McMillan & Williams Constipation Assessment Scale (0.93 vs. 0.60; p=0.944).[1] The McMillan and Williams Constipation Assessment Scale is an 8 item, 3-point questionnaire used to assess constipation symptom intensity.[12] Scores may range from 0 (no constipation) to 16 (worst possible constipation).[13]This evidence is insufficient to draw conclusions, primarily due to the small sample size and the lack of corroborating evidence.[1]

Tolterodine versus Oxybutynin

One trial published in 2015 comparing immediate release tolterodine 4 mg with immediate release oxybutynin 5 mg only focused on adverse event outcomes.[14] Based on 8 trials from a 2012 Cochrane systematic review[15] and the additional 2015 trial, tolterodine resulted in fewer withdrawals compared to oxybutynin (pooled RR 0.43, 95% CI 0.27 to 0.59; I^2=33%).[1] Incidence of dry mouth did not differ between groups (2.8% vs. 3.0%; p=0.85), and other specific adverse events of interest were not reported.[1]

Solifenacin versus Oxybutynin

One fair quality RCT (n=132) compared solifenacin 5 mg with oxybutynin IR 15 mg.[4] Mean age was 61 years (43% older than 65; 17% older than 75 years) with 78% women and 90% of subjects were White.[4] Fewer participants treated with solifenacin 5 mg daily withdrew due to adverse events than those given oxybutynin IR 15 mg daily (13% vs. 30%, RR 0.45, 95% CI 0.23 to 0.91).[1] Nine participants who took solifenacin 5 mg reported constipation compared with 4 participants who received oxybutynin IR 15 mg but this difference was not statistically significant (13% vs. 6%, RR 2.12, 95% CI 0.69 to 6.54).[1] Eight participants treated with solifenacin experienced a severe adverse event (12%) versus 18 participants treated with oxybutynin (28%), which was statistically significant (RR 0.42, 95% CI 0.20 to 0.89).[1] Of the specific adverse events of interest, only the difference in number of participants who experienced dry mouth was significant; solifenacin 5 mg (35.29%) versus oxybutynin IR 15 mg (82.81%) RR 0.43, 95% CI 0.30 to 0.60].[1] Confidence in the results of this comparison are low due to having only 1 small study comparing solifenacin to oxybutynin IR.[1]

Other OAB comparisons

No studies were identified for flavoxate, and no comparative evidence was identified for mirabegron compared with fesoterodine, darifenacin, trospium, or oxybutynin; fesoterodine compared with darifenacin, trospium, or oxybutynin; darifenacin compared with tolterodine or oxybutynin; or solifenacin compared with trospium.[1] Additionally, 1 trial which compared solifenacin with darifenacin[16] and 1 trial which compared trospium with oxybutynin and tolterodine[17] were rated poor quality due to unclear allocation concealment, blinding, and attrition and were not discussed in the DERP report.[1]

Evidence in Population Subgroups:

Diabetes

One good quality retrospective cohort study conducted using the Taiwan National Health Insurance Research Database enrolled patients with diabetes and sought to determine the risk for dementia associated with use of solifenacin, tolterodine, and oxybutynin.[5] Patients who were exposed for fewer than 28 days or who received more than 1 OAB drug or drug formulation were excluded; this resulted in 10,279 patients exposed and 592,910 patients not exposed.[1] After age and gender matching, there were 2,540 participants in each group (i.e., solifenacin, tolterodine, oxybutynin, and unexposed control group); participants were

64% male, with a mean age of 62 years.[1] The most frequent cardiovascular morbidity was hypertension (range 40% to 46%).[1] The analysis was adjusted for hypertension, lipid disorders, atrial fibrillation, chronic kidney disease, coronary artery disease, and heart failure.[1] The assessment from this study concluded risk for dementia in patients with diabetes was significantly increased with solifenacin, tolterodine and oxybutynin.[5] The adjusted hazard ratios were: solifenacin HR 2.16, 95% CI 1.81 to 2.58; tolterodine HR 2.24, 95% CI 1.85 to 2.73; and oxybutynin HR 2.35, 95% CI 1.96 to 2.81.[1] This study did not control for actual duration of drug exposure and did not formally compare the drugs with each other.[1]

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Appendix 1: Current Preferred Drug List

Route	Formulation	Brand	Generic	PDL
ORAL	SYRUP	OXYBUTYNIN CHLORIDE	oxybutynin chloride	Y
ORAL	TABLET	OXYBUTYNIN CHLORIDE	oxybutynin chloride	Y
ORAL	TAB ER 24	DITROPAN XL	oxybutynin chloride	Y
ORAL	TAB ER 24	OXYBUTYNIN CHLORIDE ER	oxybutynin chloride	Y
TRANSDERM	PATCH TDSW	OXYTROL	oxybutynin	Y
ORAL	TAB ER 24H	TOVIAZ	fesoterodine fumarate	Y
ORAL	TABLET	FLAVOXATE HCL	flavoxate HCl	N
TRANSDERM	GEL PACKET	GELNIQUE	oxybutynin chloride	N
TRANSDERM	GEL MD PMP	GELNIQUE	oxybutynin chloride	N
ORAL	TABLET	TROSPIUM CHLORIDE	trospium chloride	N
ORAL	CAP ER 24H	TROSPIUM CHLORIDE ER	trospium chloride	N
ORAL	TABLET	DETROL	tolterodine tartrate	N
ORAL	TABLET	TOLTERODINE TARTRATE	tolterodine tartrate	N
ORAL	CAP ER 24H	DETROL LA	tolterodine tartrate	N
ORAL	CAP ER 24H	TOLTERODINE TARTRATE ER	tolterodine tartrate	N
TRANSDERM	PATCH TD 4	OXYTROL FOR WOMEN	oxybutynin	N
ORAL	TABLET	VESICARE	solifenacin succinate	N
ORAL	TAB ER 24H	DARIFENACIN ER	darifenacin	N
ORAL	TAB ER 24H	ENABLEX	darifenacin	N
ORAL	TAB ER 24H	MYRBETRIQ	mirabegron	N

Drugs to Treat Overactive Bladder

Update 6 Final Report

Executive Summary

June 2018

This report is intended only for state employees in states participating in the Drug Effectiveness Review Project (DERP). Do not distribute outside your state Medicaidagency and public agency partners.

This report updates the comparative evidence on drugs for overactive bladder (OAB). The prior DERP report was a Summary Review published in 2013, a review of published systematic reviews on this topic.

Key Questions

- What is the evidence on the comparative effectiveness and harms of the OAB drugs?
- Is there evidence on whether effectiveness or harms vary in subgroups of patients?

Background

OAB is a syndrome of urinary urgency, often with urinary frequency and nocturia, in the absence of pathological factors. A subset of patients with OAB have urge urinary incontinence.

OAB is common in adults and prevalence increases with age: point prevalence ranges from 7-27% in men and 9-43% in women. Risk factors include smoking, obesity, arthritis, depression, heart disease, and irritable bowel syndrome.

The 2015 American Urological Association and the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction clinical practice guideline on OAB recommended behavioral therapies such as bladder training, pelvic floor muscle training, and fluid management, as first-line therapy, which may be combined with antimuscarinics. Antimuscarinics block acetylcholine from binding to muscarinic receptors, reducing bladder contraction. Trospium, tolterodine, oxybutynin, and fesoterodine indiscriminately bind to muscarinic receptors throughout the body, causing common adverse effects such as cognitive impairment and mouth dryness. These and other anticholinergic adverse effects contribute to low medication persistence. In contrast, solifenacin targets muscarinic receptor subtypes M_2 and M_3 specific to the detrusor muscle, and darifenacin targets only the M_3 subtype. Mirabegron mimics sympathetic activity by stimulating the β3-adrenoceptors on the detrusor muscle, promoting bladder relaxation during the filling stage.

Inclusion Criteria for Systematic Review

Populations: Adults with urge incontinence and/or overactive bladder (urgency, frequency, leakage, and dysuria).

Drugs: Listed in Table 1 below.

Comparators: Head to head

Key Outcomes: Incontinence, Urgency, Adverse Events, Other (see Full Report)

SOE: Strength of Evidence (High, Moderate, Low or Insufficient)

Table 1: Included Drugs for OAB

Names Dosage Form/Route	Approval
Darifenacin (Enablex®) Extended-release oral tablet	12/22/2004
Fesoterodine fumarate (Toviaz®) Extended-release oral tablet	10/31/2008
Flavoxate HCL (generic) Oral tablet	12/16/2004
Mirabegron (Myrbetriq®) Extended-release oral tablet	6/28/2012
Oxybutynin Cl (Ditropan XL®) Extended-release oral tablet	12/16/1998
Gelnique®; Transdermal gel	1/27/2009
Oxybutynin transdermal system (Oxytrol®) Extended-release transdermal film	2/26/2003
Solifenacin succinate (Vesicare®) Oral tablet	11/19/2004
Tolterodine tartrate (Detrol®) Oral tablet	3/25/1998
Detrol® LA Extended-release oral capsule	12/22/2000
Trospium chloride (generic) Oral tablet, extended-release oral capsule	8/13/2010

Overview of Included Evidence

For this update, we included 19 new studies - 18 head to head randomized controlled trials (RCTs) (N=11,888), and 1 observational study (N=575,671). Cumulatively, there are 42 head-to-head RCTs of drugs to treat OAB (Table 2). Trial sample sizes ranged from 60 to 2444, and 6 were rated poor quality. The majority of the RCTs were 8 to 12 weeks in duration, with 1 being 52 weeks. Most of the studies were funded by 1 of the included drug's manufacturers.

Findings

Cumulatively, this report includes 42 RCTs, 1 systematic review, and 1 cohort study – of these, 18 head-to-head trials and 1 cohort study are new in this update. See Table 2.

Table 2: Summary of Included Evidence

Drug Comparison	Prior Evidence	New Studies
Mirabegron vs. Solifenacin	0	6
Mirabegron vs. Tolterodine	1	5
Fesoterodine vs. Solifenacin	0	1
Fesoterodine vs. Tolterodine	3	0
Darifenacin vs. Solifenacin	0	1
Darifenacin vs. Trospium	0	1
Solifenacin vs. Tolterodine	5	1
Solifenacin vs. Oxybutynin	1	0
Trospium vs. Tolterodine	0	1
Trospium vs. Oxybutynin	0	1
Tolterodine vs. Oxybutynin	14	2

Note: One study is counted twice because it compared trospium to tolterodine and oxybutynin.

Mirabegron 50 mg versus Solifenacin 5 mg

No differences found at 12 weeks for incontinence episodes per 24 hours (3 RCTs), adverse event withdrawals (4 RCTs) and incidence of constipation (3 RCTs). Urgency episodes were reduced more with mirabegron than solifenacin (2 RCTs), but the difference was small (0.54 fewer episodes per 24 hours, 95% CI -0.92 to -0.16) (strength of evidence High for incontinence, Moderate for others). Dry mouth was more common with solifenacin, other anticholinergic adverse effects were not different.

Mirabegron 50 mg versus Tolterodine ER 4 mg

At 8-12 weeks, incontinence episodes were reduced more with mirabegron than tolterodine, but the difference was very small (0.15 fewer episodes per 24 hours, 95% CI -0.27 to -0.04, 5 RCTs; strength of evidence: High). No differences were found in urgency episodes (4 RCTs, strength of evidence: High) or constipation (5 RCTs, strength of evidence: Moderate), and while dry mouth was significantly more frequent with tolterodine, there were not significant differences in adverse event withdrawals (6 RCTs). A 12-month study found mirabegron to have a greater reduction in micturitions/24 hours at 12 weeks, but at 12 months tolterodine was better.

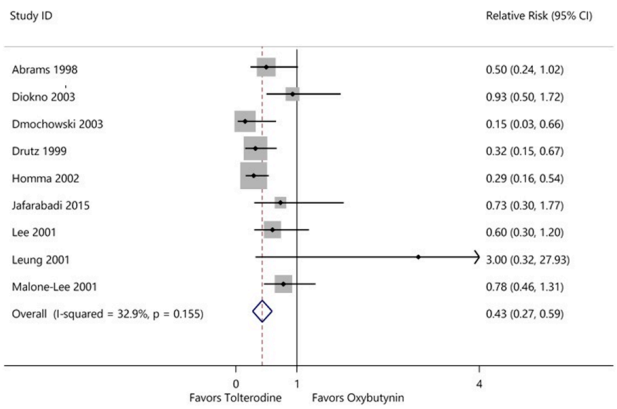
Fesoterodine 8 mg versus Tolterodine ER/IR 4 mg

Evidence from the prior report finds that fesoterodine 8 mg was associated with increased patient perception of cure or improvement, fewer leakage episodes, and fewer urgency episodes than immediate release or extended release tolterodine 4 mg (strength of evidence: High). However, absolute differences were small. Anticholinergic harms were not reported.

Tolterodine IR/ER 4 mg versus Oxybutynin IR/ER 5 – 10 mg or transdermal 3.9 mg

There was no significant difference in incontinence episodes per 24 hours (8 RCTs in prior report, strength of evidence: Moderate). Patients receiving tolterodine were less likely to withdraw due to adverse events (9 RCTs, pooled RR 0.43, 95% CI 0.27 to 0.59) (strength of evidence: Moderate, see Figure 1). No difference in the incidence of dry mouth.

Figure 1. Withdrawals due to adverse events, tolterodine versus oxybutynin



Solifenacin 5 mg versus Tolterodine IR/ER 4 mg

Evidence from the prior report found that participants treated with solifenacin were less likely to experience both incontinence (Mean Difference -0.30, 95% CI -0.53 to -0.08) and urgency episodes (Mean Difference -0.43, 95% CI -0.74 to -0.13), but the differences were small. (4 RCTs, strength of evidence: Moderate). No differences were found in adverse event

withdrawals (5 RCTs, strength of evidence: Moderate). Anticholinergic harms not reported.

Solifenacin 5 mg versus Oxybutynin IR 15 mg

No differences were found in urgency episodes (1 RCT, strength of evidence: Low). Dry mouth was more common with oxybutynin and fewer patients taking solifenacin withdrew due to adverse events (13% vs. 30%, RR 0.45, 95% CI 0.23 to 0.91). There was no difference in reports of other anticholinergic adverse effects, including constipation. (1 RCT, strength of evidence: Low)

Other comparisons were either not found, studies were rated poor quality, or evidence was insufficient to draw conclusions for any included outcome reported.

Conclusions

Cumulatively this report includes 42 RCTs, 1 systematic review, and 1 cohort study – of these 18 head-to-head trials and 1 cohort study are new in this report update. The majority of the new evidence pertains to mirabegron, with 11 new head-to-head trials (only 1 prior to this update report). Although mirabegron was found statistically better than solifenacin or tolterodine ER on a few OAB outcomes, the differences between the drugs were very small, not likely to be clinically important. For example, the difference in incontinence episodes per 24 hours was less than 1 episode between mirabegron and solifenacin. There were no differences in adverse event outcomes. Other new evidence is limited to single studies per comparison, and again any differences found in OAB outcomes were very small and not likely to be clinically important. However, both solifenacin and tolterodine were found to result in fewer adverse event withdrawals than oxybutynin. Other comparisons were either not found, studies were rated poor quality, or evidence was insufficient to draw conclusions for any included outcome reported.

DERP Systematic Review Methods

We followed systematic review methodology and procedures developed specifically for the Drug Effectiveness Review Project (DERP) and that are in accordance with current guidance for systematic reviews; for example, using dual review for study inclusion, quality assessments, and data abstraction. We searched MEDLINE and the Cochrane randomized trial database through March 2018. We requested dossiers of study information from manufacturers of included drugs, but received none. We created evidence tables, strength of evidence tables, and updated meta-analyses found in systematic reviews with newer trial data, using random effects models in Stata. Additional details on our methods can be found in Appendix A of the full report.

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Drug Class Literature Scan: Oral and Parenteral Antipsychotics

Date of Review: September 2018

Date of Last Review: Oral: 3/2018; Parenteral: 9/2017
Literature Search: 4/1/17 – 5/31/18

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

Conclusions:

- Five recent systematic reviews are included in this literature scan of recent evidence for antipsychotic safety and efficacy. No new guidelines or Food and Drug Administration (FDA) safety alerts have been published since the last class update.
- Three separate Cochrane reviews evaluated evidence for the use of intramuscular haloperidol, intramuscular aripiprazole, and oral risperidone to manage psychosis-induced aggression or agitation for rapid tranquilization.[1-3] Outcomes of interest included tranquilization or time to sleep onset within 30 minutes, repeated need for rapid tranquilization within 24 hours, and adverse effects. In the 2 trials that compared haloperidol versus aripiprazole, people in the haloperidol group required fewer injections; this difference was statistically significant (pooled Relative Risk (RR) 0.78, 95% Confidence Interval (CI) 0.62 to 0.99).[1] More people in the haloperidol group experienced dystonia compared to aripiprazole (pooled RR 6.63, 95% CI 1.52 to 28.86). The risperidone review found risperidone was no better or worse than haloperidol or olanzapine for calming aggression within 24 hours.[3]
- Limited data from small studies assessing treatments for tardive dyskinesia (TD) including antipsychotic reduction, antipsychotic discontinuation, or specific antipsychotic drugs did not provide convincing evidence of the value of these approaches in alleviating dyskinesia.[4]
- A 2017 systematic review and meta-analysis analyzed randomized control trial (RCT) data comparing long-acting injectable antipsychotics (LAI) to the oral formulation of the same medication to determine if route of administration impacted efficacy or tolerability.[5] The primary outcome was the overall dropout rate for any reason from antipsychotic therapy. For risperidone, olanzapine, fluphenazine, and haloperidol the number of overall dropouts did not differ between oral or LAI formulations.[5] A small effect in favor of LAI aripiprazole was observed in 2 trials (RR 0.78; 95% CI 0.64 to 0.95; Absolute Risk Reduction (ARR) 7%; Number Needed to Treat (NNT) 14).[5] No differences between oral and LAI formulations emerged in terms of dropouts for specific reasons including adverse events, extrapyramidal symptoms, prolactin increase, weight gain, non-response rate, or relapse rate.[5]
- Latuda (lurasidone) received an expanded indication in 10 to 17 year olds with major depressive episode associated with bipolar 1 disorder (bipolar depression) as of March 2018.[6] The efficacy of lurasidone in pediatric patients aged 10 to 17 years was established in a 6-week, multicenter, randomized, double-blind, placebo-controlled study of patients who met Diagnostic and Statistical Manual (DSM)-5 criteria for a major depressive episode associated with bipolar I disorder.[7] The primary efficacy endpoint used to assess depressive symptoms, the mean change in Children's Depression Rating Scale, Revised (CDRS-R) total score (range 17 to 113 points) at 6 weeks, was significantly greater in the lurasidone group compared to placebo (-21.0 versus -15.3; $p < 0.0001$; effect size 0.45).[7]
- The November 1, 2017 ISMP Quarter Watch publication summarized reported adverse events (AEs) for pimavanserin through March 2017.[8] Of the 2236 reported events with pimavanserin, the most frequently reported AEs were: hallucinations (21.8%), ineffective drug (14.9%), confusional state (11.5%), and

death (10.9%).[8] Further analysis indicated pimavanserin may be making some psychosis worse, or in other instances, was not providing the expected benefit.[8] The FDA is continuing to monitor these reports, but has not revised labeling for pimavanserin to date.

- A new formulation of long-acting aripiprazole lauroxil, Aristada Initio™, designed for administration as a one-time injection at the start of LAI antipsychotic therapy received FDA approval in July 2018. Aristada Initio™ is designed to provide an extended-release formulation using a smaller particle size of aripiprazole lauroxil compared to Aristada®, thereby enabling faster dissolution and leading to more rapid achievement of therapeutic levels of aripiprazole.[9] Previously, the standard initiation regimen for long acting aripiprazole injection included 21 consecutive days of oral aripiprazole starting with the first long acting injection of Aristada®. According to the manufacturer, the Aristada Initio™ regimen provides patients with relevant levels of aripiprazole within four days of initiation.[9]
- The FDA approved a new once-monthly subcutaneous formulation of risperidone (Perseris™) for the treatment of schizophrenia in adults in July 2018. Perseris™ uses an extended-release delivery system to form a subcutaneous depot that provides sustained levels of risperidone over 1 month.[10] According to the manufacturer, clinically relevant levels of the drug are reached after the first 90 mg or 120 mg injection without use of a loading dose or any supplemental oral dose of risperidone.[10] The efficacy of once-monthly subcutaneous risperidone injection was demonstrated in a phase 3 randomized, double-blind, placebo-controlled, 8-week study of 354 patients.[10]

Recommendations:

- No changes to the PDL are recommended for oral or parenteral antipsychotics based on efficacy or safety data.
- Evaluate comparative costs in executive session.

Summary of Prior Reviews and Current Policy

In the Oregon Health Plan, antipsychotic medications are exempt from traditional preferred drug list (PDL) and PA requirements. However, clinical PA criteria which address safety concerns or medically inappropriate use may be implemented. Currently, safety edits are implemented for low dose quetiapine to prevent off-label use and for pimavanserin to promote safe use in patients with Parkinson's disease psychosis. The PA criteria for these safety edits are outlined in **Appendix 5**. The majority of antipsychotic use in the Oregon Medicaid population is for oral second generation antipsychotics (SGA) including aripiprazole, quetiapine, risperidone, and olanzapine. Approximately 4% of antipsychotic medication claims are for parenteral formulations. Paliperidone, aripiprazole, and haloperidol are the most frequently prescribed injectable agents in this class. Each quarter, approximately 25,000 patients receive a prescription for a SGA and 1700 patients have claims for a first generation antipsychotic. The antipsychotics included on the Oregon PDL are presented in **Appendix 1**.

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), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Institute for Clinical and Economic Review (ICER), 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. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

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

New Systematic Reviews:
After review, 21 systematic reviews were excluded due to poor quality, wrong study design of included trials (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical).

Haloperidol, aripiprazole and risperidone for emergent use in patients with agitation due to psychosis
Three separate Cochrane reviews evaluated evidence for the use of intramuscular haloperidol, intramuscular aripiprazole, and oral risperidone to manage psychosis-induced aggression or agitation for rapid tranquilization.[1-3] Outcomes of interest included tranquilized or asleep by 30 minutes, repeated need for rapid tranquilization within 24 hours, and adverse effects. The 2017 haloperidol review was an update of a 2012 Cochrane publication and identified nine new RCTs.[1] Most of the trials were small and carried considerable risk of bias.[1] The authors reported no conflicts of interest. In the 2 trials that compared haloperidol versus aripiprazole, people in the haloperidol group required fewer injections; this difference was statistically significant(2 RCTS, n=473, pooled RR 0.78, 95% CI 0.62 to 0.99).[1] However, more people in the haloperidol group experienced dystonia compared to aripiprazole (2 RCTs, pooled RR 6.63, 95% CI 1.52 to 28.86).[1] In trials that compared haloperidol with lorazepam, no significant differences were found with regard to number of participants asleep at one hour (1 RCT, n=60, RR 1.05, 95% CI 0.76 to 1.44) or those requiring additional injections (1 RCT, n=66, RR 1.14, 95% CI 0.91 to 1.43).[1] The adverse effects of haloperidol (e.g. dystonia) were not offset by the addition of lorazepam (1 RCT, n=67, RR 8.25, 95% CI 0.46 to 147.45).[1] In comparative trials of haloperidol and olanzapine, significantly more people in the olanzapine group were asleep in 2 hours compared with those allocated haloperidol (1 RCT, n = 257, RR 1.16, 95% CI 1.02 to 1.32).[1] Addition of promethazine to haloperidol was investigated in two trials (n=376).[1] More people in the haloperidol group compared to the combination group were not tranquilized or asleep by 20 minutes (1 RCT, n=316, RR 1.60, 95% CI 1.18 to 2.16).[1] Acute dystonia was too common in the haloperidol alone group for the trial to continue beyond the interim analysis (1 RCT, n=316, RR 19.48, 95% CI 1.14 to 331.92).[1] Evidence for rapid tranquilization in agitated patients supports the use of haloperidol combined with promethazine; the 2015 update of United Kingdom's National Institute for Health and Care Excellence (NICE) guidelines on short term management of aggression recommends this strategy as well.[11]

The aripiprazole review was based on a literature search from December 2014 through April 2017. Three trials (n=707) were included in this systematic review. The evidence was graded as low quality due to limited comparisons and small size of trials.[3] No trials reported useful data for the primary outcomes of tranquilized or time to sleep onset by 30 minutes. The aripiprazole versus haloperidol trials were previously described in the haloperidol summary. Compared to aripiprazole, olanzapine was better at reducing agitation based on the Positive and Negative Syndrome Scale-Excited Component (PANSS-EC) score (1 RCT, n=80, RR 0.77, 95% CI 0.60 to 0.99) at two hours.[2] No differences were found between aripiprazole and olanzapine in the number of people experiencing at least one adverse effect within 24 hours of treatment (1 RCT, n=80, RR 0.75, 95% CI 0.45 to 1.24).[2] However, participants allocated to aripiprazole experienced less somnolence compared to olanzapine (1 RCT, n=80, RR 0.25, 95% CI 0.08 to 0.82).[2]

The literature search for the oral risperidone review was compiled through April 2017.[3] This systematic review contains data from five trials (total n=221) comparing risperidone to haloperidol, olanzapine, and quetiapine.[3] None of the included studies provided useable data on the primary outcome tranquilization or asleep by 30 minutes, or repeated need for tranquilization.[3] Data were available for the other main outcomes of agitation or aggression, needing restraint, and incidence of adverse effects.[3] Due to risk of bias, small size of trials, and indirectness of outcome measures, evidence was graded as low quality.[3] No clear difference was found between oral risperidone and haloperidol (oral or intramuscular) for reduction of agitation, measured as at least 50% reduction in the Positive and Negative Syndrome Scale-Psychotic Agitation Sub-score (PANSS-PAS) (RR 1.04, 95% CI 0.86 to 1.26; n=124), and no effect was observed for the need to use restraints (RR

2.00, 95% CI 0.43 to 9.21; n=28).[3] Incidence of adverse effects was similar between treatment groups (RR 0.94, 95% CI 0.54 to 1.66; n=124).[3] One small trial (n=29) compared oral risperidone to oral olanzapine. No difference was observed between risperidone or olanzapine for either agitation measured as PANSS-PAS endpoint score at two hours MD 2.50, 95% CI -2.46 to 7.46); the need to use restraints at four days (RR 1.43, 95% CI 0.39 to 5.28); or specific movement disorders measured as Behavioral Activity Rating Scale endpoint score at four days (MD 0.20, 95% CI -0.43 to 0.83).[3] There was no difference between risperidone and quetiapine for incidence of akathisia after 24 hours (RR 1.67, 95% CI 0.46 to 6.06).[3] In summary, this Cochrane review found risperidone was no better or worse than haloperidol or olanzapine for calming aggression within 24 hours, and two weeks after treatment, people receiving risperidone had worse scores on scales measuring levels of aggression than those receiving quetiapine.[3]

Treatment strategies for tardive dyskinesia

Some proposed strategies for alleviating tardive dyskinesia (TD) include antipsychotic cessation, dose reduction, or switch to a different medication. The focus of a 2018 Cochrane update evaluated evidence from 8 RCTs for the management of TD using these 3 strategies.[4] Due to small sample sizes and short trial duration most outcomes were rated as low quality evidence.[4] No clinically important improvement in TD severity was associated with antipsychotic dose reduction versus antipsychotic maintenance at 44 to 48 weeks (2 RCTs, n=17, RR 0.42 95% CI 0.17 to 1.04).[4] None of the 5 trials (n=140) that evaluated switching to another antipsychotic found a clinically important difference in improving TD symptoms.[4] Specifically, there was no evidence of a difference in TD symptoms for switch to risperidone or haloperidol compared with antipsychotic cessation (RR 1 RCT, n=48, RR 2.08 95% CI 0.74 to 5.86) or switch to risperidone compared with switch to haloperidol (RR 1 RCT, n=37, RR 0.68 95% CI 0.34 to 1.35).[4] Limited data from small studies using antipsychotic reduction or specific antipsychotic drugs as treatments for TD did not provide any convincing evidence of the value of these approaches.[4]

Safety and efficacy of oral antipsychotics compared to long-acting injectable antipsychotics

A 2017 systematic review and meta-analysis analyzed RCT data from long-acting injectable antipsychotics (LAI) compared to the oral formulation of the same medication to determine if route of administration had an impact on efficacy or tolerability.[5] Literature was searched through July 2016. Twenty studies were included in the review and data from 17 RCTs contributed to the meta-analysis for the following antipsychotics: risperidone (n=6), olanzapine (n=2), aripiprazole (n=3), fluphenazine (n=7) and haloperidol (n=2).[5] For the primary outcome of overall treatment discontinuation, quality of evidence was high for aripiprazole, moderate for risperidone, low for haloperidol, and very low for olanzapine and fluphenazine.[5] For all drugs, the number of dropouts for any reason did not differ between the two formulations, except for a small effect in favor of LAI aripiprazole (2 RCTs; 986 patients; RR 0.78; 95% CI 0.64 to 0.95; ARR 7%; NNT 14).[5] Similarly, no differences between oral and LAI formulations emerged in terms of dropouts for adverse events, extrapyramidal symptoms, prolactin increase, weight gain, non-response rate, and relapse rate.[5]

New Guidelines: No new guidelines have been published since the last class update.

New Formulations or Indications:

1.Latuda (lurasidone) received an expanded indication to 10-17 year olds with major depressive episode associated with bipolar 1 disorder (bipolar depression) as of March 2018.[6] Previously, lurasidone was only FDA approved for use in adults with bipolar depression. The efficacy of lurasidone in pediatric patients aged 10 to 17 years was established in a 6-week, multicenter, randomized, double-blind, placebo-controlled study of patients who met DSM-5 criteria for a major depressive episode associated with bipolar I disorder, with or without rapid cycling, and without psychotic features (N=343).[7] Patients were randomized to flexibly dosed lurasidone 20 to 80 mg/day or placebo. At the end of the clinical study, most patients (67%) received 20 mg/day or 40 mg/day.[7] The primary rating scale used to assess depressive symptoms in this study was the CDRS-R total score. The CDRS-R is a 17-item clinician rated scale with total scores ranging from 17 to 113.[12] A score of greater than 40 is indicative of depression, whereas a score less than 28 is often used to define remission (minimal or no symptoms).[12] The

primary endpoint was the mean change from baseline in CDRS-R score to week 6.[7] The least squares mean change in CDRS-R total score was significantly greater in the lurasidone group compared to the placebo group (-21.0 versus -15.3; p < 0.0001; effect size 0.45) at week 6.[7] Treatment response was defined as ≥50% reduction from baseline to week 6 in CDRS-R total score (after subtracting 17 points from the total score to adjust for the scale range).[7] The percent of participants meeting a priori response criteria was significantly larger in the lurasidone group compared with the placebo group at week 6 (59.5% versus 36.5%; *p* < .0001; NNT = 5).[7] The 2 most common adverse events observed in patients taking lurasidone were nausea and somnolence.[7] Least squares mean change at week 6 in body weight was similar for the lurasidone and placebo groups (+0.74 versus +0.44 kg), and a similar percent of patients on lurasidone versus placebo had at least 7% weight gain (4.0% versus 5.3%).[7] There were no clinically meaningful differences between lurasidone and placebo groups in change in lipid, glucose, and prolactin levels.[7]

2. Alkermes, Inc. developed a new formulation of long-acting aripiprazole lauroxil, Aristada Initio™, designed for administration as a one-time injection at the start of LAI antipsychotic therapy which received FDA approval in July 2018. Aristada Initio™ uses proprietary NanoCrystal® technology and is designed to provide an extended-release formulation using a smaller particle size of aripiprazole lauroxil compared to Aristada®, thereby enabling faster dissolution and leading to more rapid achievement of therapeutic levels of aripiprazole.[13] Previously, the standard initiation regimen for long acting aripiprazole injection included 21 consecutive days of oral aripiprazole starting with the first long acting injection of Aristada®. According to the manufacturer, the Aristada Initio™ regimen provides patients with relevant levels of aripiprazole within four days of initiation.[13] Therapy is started with aripiprazole lauroxil extended-release 675 mg intramuscular injection administered by a health care professional in conjunction with aripiprazole 30mg orally as a one-time dose.[13] For patients naïve to aripiprazole, tolerability to the drug should be established with oral therapy before transitioning to LAI formulations.[13] Aristada Initio™ is not interchangeable with other aripiprazole LAI formulations due to different pharmacokinetic profiles and is not approved for repeated dosing.[13] Aristada Initio™ may also be administered as a single dose for patients re-starting therapy after missing a dose of Aristada®.[13] The first Aristada® injection (441 mg, 662 mg, 8821 mg or 1064 mg) may be administered on the same day as an Aristada Initio™ dose at different injection sites or 10 days afterwards.[13] A pharmacokinetic bridging study demonstrated that an intramuscular injection of Aristada®, a 30 mg dose of oral aripiprazole, and a single 675 mg dose of Aristada Initio™ resulted in aripiprazole concentrations comparable to Aristada® treatment initiated with 21 days of oral aripiprazole.[13] A single strength of Aristada Initio (i.e., 675 mg) was adequate for all dose levels of oral aripiprazole and Aristada LAI.[13] Aristada Initio™ was evaluated for safety in 170 adult patients with schizophrenia and was found to have similar side effects to Aristada®.[13] The efficacy of Aristada Initio™ was based on previous trials of the aripiprazole LAI formulation (Aristada®).[13]

3. The FDA approved a new once-monthly subcutaneous formulation of risperidone (Perseris™) for the treatment of schizophrenia in adults. Perseris™ uses an extended-release delivery system to form a subcutaneous depot that provides sustained levels of risperidone over 1 month.[10] According to the manufacturer, clinically relevant levels of the drug are reached after the first 90 mg or 120 mg injection without use of a loading dose or any supplemental oral dose of risperidone.[10] The efficacy of once-monthly subcutaneous risperidone injection was demonstrated in a phase 3 randomized, double-blind, placebo-controlled, 8-week study of 354 patients.[10] The study showed a statistically significant improvement in the Positive and Negative Syndrome Scale total score and the Clinical Global Impression Severity of Illness at day 57.[10] The clinical trials of Perseris™ were designed for the antipsychotic to be started without a loading dose or any supplemental risperidone. The systemic safety profile of Perseris was consistent with the known safety profile of oral risperidone.[10] The most common systemic adverse reactions were increased weight, sedation/somnolence, and musculoskeletal pain. The most common injection site reactions were injection site pain and reddening of the skin. Perseris™ has a boxed warning noting that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk for death.[10] Perseris is not approved for use in patients with dementia-related psychosis. This new formulation is not scheduled to arrive in pharmacies until the fourth quarter of 2018.

New Safety Alerts:

Food and Drug Administration: No new FDA safety alerts have been reported.

Institute for Safe Medication Practices (ISMP)

The November 1, 2017 ISMP Quarter Watch publication summarized reported adverse events (AEs) for pimavanserin through March 2017.[8] Of the 2236 reported events with pimavanserin, the most frequently reported AEs were: hallucinations (21.8%), ineffective drug (14.9%), confusional state (11.5%), and death (10.9%).[8] Further analysis indicated that the drug may make some psychosis worse, or in other instances, may not providing the expected benefit.[8] The number of reports of hallucinations was large (n=487), with 73% of incidents observed by health professionals, who could be expected to understand that hallucinations occur in 20-70% of Parkinson's patients.[8] The numerous reports that the drug was ineffective are consistent with the limited benefits observed in the clinical trials.[8] This first substantial group of pimavanserin adverse event reports disclosed an additional safety issue: ISMP identified 318 cases where pimavanserin, which blocks serotonin signaling, was combined with quetiapine or other antipsychotics that block dopamine signaling.[8] Antipsychotics are not recommended for use in the elderly, and are not approved for use in Parkinson's Disease.[8] In the clinical trials for pimavanserin, use of quetiapine or other antipsychotics was one of the exclusion criteria.[14] The FDA is continuing to monitor these reports, but has not revised labeling for pimavanserin to date.

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Appendix 1: Current Preferred Drug List

Oral Antipsychotics, 1st Generation

Route	Formulation	Brand	Generic	PDL	Carveout
ORAL	ELIXIR	FLUPHENAZINE HCL	fluphenazine HCl	Y	Y
ORAL	ORAL CONC	FLUPHENAZINE HCL	fluphenazine HCl	Y	Y
ORAL	TABLET	FLUPHENAZINE HCL	fluphenazine HCl	Y	Y
ORAL	TABLET	PERPHENAZINE	perphenazine	Y	Y
ORAL	TABLET	TRIFLUOPERAZINE HCL	trifluoperazine HCl	Y	Y
ORAL	TABLET	THIORIDAZINE HCL	thioridazine HCl	Y	Y
ORAL	ORAL CONC	HALOPERIDOL LACTATE	haloperidol lactate	Y	Y
ORAL	TABLET	HALOPERIDOL	haloperidol	Y	Y
ORAL	CAPSULE	THIOTHIXENE	thiothixene	Y	Y
ORAL	CAPSULE	LOXAPINE	loxapine succinate	Y	Y
ORAL	TABLET	CHLORPROMAZINE HCL	chlorpromazine HCl	V	Y
ORAL	TABLET	ORAP	pimozide	V	Y
ORAL	TABLET	PIMOZIDE	pimozide	V	Y
INHALATION	AER POW BA	ADASUVE	loxapine	V	Y

Oral Antipsychotics, 2nd Generation

Route	Formulation	Brand	Generic	PDL	Carveout
ORAL	TABLET	CLOZAPINE	clozapine	Y	Y
ORAL	TABLET	CLOZARIL	clozapine	Y	Y
ORAL	TABLET	RISPERDAL	risperidone	Y	Y
ORAL	TABLET	RISPERIDONE	risperidone	Y	Y
ORAL	SOLUTION	RISPERDAL	risperidone	Y	Y
ORAL	SOLUTION	RISPERIDONE	risperidone	Y	Y
ORAL	TABLET	OLANZAPINE	olanzapine	Y	Y
ORAL	TABLET	ZYPREXA	olanzapine	Y	Y
ORAL	TABLET	QUETIAPINE FUMARATE	quetiapine fumarate	Y	Y
ORAL	TABLET	SEROQUEL	quetiapine fumarate	Y	Y
SUBLINGUAL	TAB SUBL	SAPHRIS	asenapine maleate	Y	Y
ORAL	TABLET	LATUDA	lurasidone HCl	Y	Y
ORAL	TAB RAPDIS	CLOZAPINE ODT	clozapine	V	Y
ORAL	TAB RAPDIS	FAZACLO	clozapine	V	Y
ORAL	TAB RAPDIS	RISPERIDONE ODT	risperidone	V	Y
ORAL	TAB RAPDIS	OLANZAPINE ODT	olanzapine	V	Y
ORAL	TAB RAPDIS	ZYPREXA ZYDIS	olanzapine	V	Y
ORAL	TAB ER 24H	QUETIAPINE FUMARATE ER	quetiapine fumarate	V	Y
ORAL	TAB ER 24H	SEROQUEL XR	quetiapine fumarate	V	Y

ORAL	CAPSULE	GEODON	ziprasidone HCl	V	Y
ORAL	CAPSULE	ZIPRASIDONE HCL	ziprasidone HCl	V	Y
ORAL	TAB ER 24	INVEGA	paliperidone	V	Y
ORAL	TAB ER 24	PALIPERIDONE ER	paliperidone	V	Y
ORAL	TABLET	ABILIFY	aripiprazole	V	Y
ORAL	TABLET	ARIPIPRAZOLE	aripiprazole	V	Y
ORAL	SOLUTION	ARIPIPRAZOLE	aripiprazole	V	Y
ORAL	TAB RAPDIS	ARIPIPRAZOLE ODT	aripiprazole	V	Y
ORAL	TABLET	REXULTI	brexpiprazole	V	Y
ORAL	CAPSULE	VRAYLAR	cariprazine HCl	V	Y
ORAL	CAP DS PK	VRAYLAR	cariprazine HCl	V	Y

Parenteral Antipsychotics

Route	Formulation	Brand	Generic	PDL	Carveout
INJECTION	AMPUL	CHLORPROMAZINE HCL	chlorpromazine HCl	Y	Y
INJECTION	VIAL	FLUPHENAZINE DECANOATE	fluphenazine decanoate	Y	Y
INJECTION	VIAL	FLUPHENAZINE HCL	fluphenazine HCl	Y	Y
INTRAMUSC	AMPUL	HALDOL DECANOATE 50	haloperidol decanoate	Y	Y
INTRAMUSC	AMPUL	HALOPERIDOL DECANOATE	haloperidol decanoate	Y	Y
INTRAMUSC	VIAL	HALOPERIDOL DECANOATE	haloperidol decanoate	Y	Y
INTRAMUSC	AMPUL	HALDOL DECANOATE 100	haloperidol decanoate	Y	Y
INTRAMUSC	AMPUL	HALOPERIDOL DECANOATE 100	haloperidol decanoate	Y	Y
INJECTION	AMPUL	HALDOL	haloperidol lactate	Y	Y
INJECTION	AMPUL	HALOPERIDOL	haloperidol lactate	Y	Y
INJECTION	VIAL	HALOPERIDOL LACTATE	haloperidol lactate	Y	Y
INTRAMUSC	SYRINGE	RISPERDAL CONSTA	risperidone microspheres	Y	Y
INTRAMUSC	SUSER VIAL	ABILIFY MAINTENA	aripiprazole	Y	Y
INTRAMUSC	SUSER SYR	ABILIFY MAINTENA	aripiprazole	Y	Y
INTRAMUSC	SUSER SYR	ARISTADA	aripiprazole lauroxil	Y	Y
INTRAMUSC	VIAL	OLANZAPINE	olanzapine	V	Y
INTRAMUSC	VIAL	ZYPREXA	olanzapine	V	Y
INTRAMUSC	VIAL	GEODON	ziprasidone mesylate	V	Y
INTRAMUSC	SYRINGE	INVEGA SUSTENNA	paliperidone palmitate	V	Y
INTRAMUSC	SYRINGE	INVEGA TRINZA	paliperidone palmitate	V	Y
INTRAMUSC	VIAL	ZYPREXA RELPREVV	olanzapine pamoate	V	Y
INTRAMUSC	SYRINGE	ARISTADA INITIO	aripiprazole lauroxil, submicronized, ER	V	Y

Appendix 2: New Comparative Clinical Trials

A total of 249 citations were manually reviewed from the initial literature search. After further review, 247 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining trials are summarized in the table below. The full abstracts are included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

<table>
<tr><th>Study</th><th>Comparison</th><th>Population</th><th>Primary Outcome</th><th>Results</th></tr>
<tr><td>Nemeth G, et al.[15]

DB, MC, RCT

n = 460

Duration: 32 weeks</td><td>1.Cariprazine 3mg, 4.5 mg, or 6mg per day

vs.

2.Risperidone 3mg, 4mg, or 6mg per day

4 week lead-in period followed by 26 week DB treatment and 2 week safety follow-up</td><td>Adults aged 18-65 years with stable schizophrenia (> 2 years) with predominant negative symptoms (> 6 months)</td><td>Change from baseline to week 26 on the PANSS-FSNS</td><td>Least squares mean change in PANSS-FSNS:
1. Cariprazine -8.90 points (n=230)
2. Risperidone -7.44 points (n=230)

Least squares mean difference −1.46; 95% CI −2.39 to −0.53; p=0.0022</td></tr>
<tr><td>Nicol G, et al.[16]

OL, RCT

N = 144

Duration: 12 weeks</td><td>1.Aripiprazole 6 mg po (mean dose)

Vs.

2. Olanzapine 6 mg po (mean dose)

Vs.

3.Risperidone 1 mg po (mean dose)</td><td>Antipsychotic-naive youths aged 6 to 18 years
with 1 or more Axis I DSM IV diagnosis and clinically significant aggression defined by a score of at least 18 on the Irritability subscale of the Aberrant Behavior Checklist</td><td>Treatment effects over 12 weeks on total body fat (mean DXA percentage)
as well as insulin sensitivity at muscle</td><td>
<table>
<tr><th>Variable</th><th>Risperidone</th><th>Olanzapine</th><th>Aripiprazole</th></tr>
<tr><td>Change in DXA Body Fat from Week 0 to Week 12</td><td>1.81%

95% CI 0.91 to 2.71</td><td>4.12%

95% CI 3.16 to 5.08</td><td>1.66 %

95% CI 0.86 to 2.46</td></tr>
<tr><td>p value</td><td>< 0.001</td><td><0.001</td><td><0.001</td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td>Insulin-stimulated change in glucose rate of disappearance</td><td>2.30%

95% CI -24.04 to 28.64</td><td>-29.34%

95% CI -58.53 to -0.15</td><td>-30.26

95% CI -50.5 to -9.97</td></tr>
<tr><td>p value</td><td>0.87</td><td>0.06</td><td>0.006</td></tr>
</table>
</td></tr>
</table>

Abbreviations: CI = Confidence Interval; DB =Double Blind; MC = Multi-Center, OL = Open Label; PANSS-FSNS = Positive and Negative Syndrome Scale Factor Score for Negative Symptoms; PO = Oral; RCT = Randomized Clinical Trial

Appendix 3: Abstract of Comparative Clinical Trials

1.Nemeth G, Laszlovszky I, Czobor P, et al. Cariprazine versus risperidone monotherapy for treatment of predominant negative symptoms in patients with schizophrenia: a randomised, double-blind, controlled trial. Lancet.389 (10074):1103-1113.

BACKGROUND: Although predominant negative symptoms of schizophrenia can be severe enough to cause persistent impairment, effective treatment options are lacking. We aimed to assess the new generation antipsychotic cariprazine in adult patients with predominant negative symptoms.
METHODS: In this randomised, double-blind, phase 3b trial, we enrolled adults aged 18-65 years with long-term (>2 year), stable schizophrenia and predominant negative symptoms (>6 months) at 66 study centres (mainly hospitals and university clinics, with a small number of private practices) in 11 European countries. Patients were randomly assigned (1:1) by an interactive web response system to 26 weeks of monotherapy with fixed-dose oral cariprazine (3 mg, 4·5 mg [target dose], or 6 mg per day) or risperidone (3 mg, 4 mg [target dose], or 6 mg per day); previous medication was discontinued over 2 weeks. The primary outcome was change from baseline to week 26 or end of treatment on the Positive and Negative Syndrome Scale factor score for negative symptoms (PANSS-FSNS) analysed in a modified intention-to-treat population of patients who had follow-up assessments within 5 days after last receipt of study drugs with a mixed-effects model for repeated measures. Safety was assessed in all patients who received at least one dose of study drug. This study is registered with EudraCT, number 2012-005485-36.
FINDINGS: Between May 27, 2013, and Nov 17, 2014, 533 patients were screened and 461 (86%) patients were randomised to treatment (230 for cariprazine and 231 for risperidone); 460 were included in the safety population (one patient discontinued before study drug intake). 227 (99%) of 230 patients in the cariprazine group and 229 (99%) of 230 patients in the risperidone group were included in the modified intention-to-treat population (178 [77%] in each group completed 26 weeks of treatment). Mean daily doses were 4·2 mg (SD 0·6) for cariprazine and 3·8 mg (0·4) for risperidone. Treatment-emergent adverse events (eg, insomnia, akathisia, worsening of schizophrenia, headache, and anxiety) were reported in 123 (54%) patients treated with cariprazine and 131 (57%) patients treated with risperidone. Use of cariprazine led to a greater least squares mean change in PANSS-FSNS from baseline to week 26 than did risperidone (-8·90 points for cariprazine vs -7.44 points for risperidone; least squares mean difference -1.46, 95% CI -2.39 to -0.53; p=0.0022; effect size 0.31). One patient in the risperidone group died of a cause regarded as unrelated to treatment.
INTERPRETATION: Our results support the efficacy of cariprazine in the treatment of predominant negative symptoms of schizophrenia.
FUNDING: Gedeon Richter Plc.

2. Nicol GE, Yingling MD, Flavin KS, et al. Metabolic effects of antipsychotics on adiposity and insulin sensitivity in youths: A randomized clinical trial. JAMA psychiatry. 2018.

OBJECTIVE: To characterize the metabolic effects of first exposure to antipsychotics in youths using criterion standard assessments of body composition and insulin sensitivity.
DESIGN, SETTING, AND PARTICIPANTS: This randomized clinical trial recruited antipsychotic-naive youths aged 6 to 18 years in the St Louis, Missouri, metropolitan area who were diagnosed with 1 or more psychiatric disorders and clinically significant aggression and in whom antipsychotic treatment was considered. Participants were enrolled from June 12, 2006, through November 10, 2010. Enrolled participants were randomized (1:1:1) to 1 of 3 antipsychotics commonly used in children with disruptive behavioral disorders and evaluated for 12 weeks. Data were analyzed from January 17, 2011, through August 9, 2017.
INTERVENTIONS: Twelve weeks of treatment with oral aripiprazole (n = 49), olanzapine (n = 46), or risperidone (n = 49).
MAIN OUTCOMES AND MEASURES: Primary outcomes included percentage total body fat measured by dual-energy x-ray absorptiometry (DXA) and insulin sensitivity in muscle measured via hyperinsulinemic clamps with stable isotopically labeled tracers. Secondary outcomes included abdominal adiposity measured by magnetic resonance imaging (MRI) and adipose and hepatic tissue insulin sensitivity measured via clamps with tracers.
RESULTS: The intention-to-treat sample included 144 participants (98 males [68.1%]; mean [SD] age, 11.3 [2.8] years); 74 (51.4%) were African American, and 43 (29.9%) were overweight or obese at baseline. For the primary outcomes, from baseline to week 12, DXA percentage total body fat increased by 1.18% for risperidone, 4.12% for olanzapine, and 1.66% for aripiprazole and was significantly greater for olanzapine than risperidone or aripiprazole (time by treatment interaction P < .001). From baseline to week 12, insulin-stimulated change in glucose rate of disappearance increased by 2.30% for risperidone and decreased by 29.34% for olanzapine and 30.26% for aripiprazole, with no significant difference across medications (time by treatment interaction, P < .07). This primary measure of insulin sensitivity decreased significantly during 12 weeks in the

pooled study sample (effect of time, F = 17.38; P < .001). For the secondary outcomes from baseline to week 12, MRI measured abdominal fat increased, with subcutaneous fat increase significantly greater for olanzapine than risperidone or aripiprazole (time by treatment, P = .003). Behavioral improvements occurred with all treatments.
CONCLUSIONS AND RELEVANCE: Adverse changes in adiposity and insulin sensitivity were observed during 12 weeks of antipsychotic treatment in youths, with the greatest fat increases on olanzapine. Such changes, likely attributable to treatment, may be associated with risk for premature cardiometabolic morbidity and mortality. The results inform risk-benefit considerations for antipsychotic use in youths.

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to May Week 4 2018, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations May 31, 2018

1 exp CHLORPROMAZINE/	17141
2 exp HALOPERIDOL/	15380
3 exp FLUPHENAZINE/	2391
4 exp ARIPIPRAZOLE/	2032
5 exp Paliperidone Palmitate/	700
6 exp RISPERIDONE/	5844
7 olanzapine.mp.	7479
8 exp PERPHENAZINE/	1560
9 exp Trifluoperazine/	3554
10 exp Thioridazine/	2348
11 exp THIOTHIXENE/	333
12 exp LOXAPINE/	604
13 exp PIMOZIDE/	1687
14 exp CLOZAPINE/	7648
15 exp Quetiapine Fumarate/	2528
16 asenapine maleate.mp.	15
17 exp Lurasidone Hydrochloride/	177
18 ziprasidone HCl.mp.	5
19 brexpiprazole.mp.	70
20 cariprazine.mp.	79
21 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	59162

22 limit 22 to (english language and humans and yr="2017 -Current" and (clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta-analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews))
248

Low Dose Quetiapine

Goal(s):
- To promote and ensure use of quetiapine that is supported by the medical literature.
- To discourage off-label use for insomnia.
- Promote the use of non-pharmacologic alternatives for chronic insomnia.

Initiative:
- Low dose quetiapine (Seroquel® and Seroquel XR®)

Length of Authorization:
- Up to 12 months (criteria-specific)

Requires PA:
- Quetiapine (HSN = 14015) doses ≤50 mg/day
- Auto PA approvals for :
  - Patients with a claim for a second generation antipsychotic in the last 6 months
  - Patients with prior claims evidence of schizophrenia or bipolar disorder
  - Prescriptions identified as being written by a mental health provider

Covered Alternatives:
- Preferred alternatives listed at www.orpdl.org/drugs/
- Zolpidem is available for short-term use (15 doses/30 days) without PA.

Table 1. Adult (age ≥18 years) FDA-approved Indications for Quetiapine

Bipolar Disorder	F3010; F302; F3160-F3164; F3177-3178; F319	
Major Depressive Disorder	F314-315; F322-323; F329; F332-333; F339; ~~F3130~~	For Seroquel XR® only, Adjunctive therapy with antidepressants for Major Depressive Disorder
Schizophrenia	F205; F209; F2081; F2089	
Bipolar Mania	F3010; F339; F3110-F3113; F312	

Bipolar Depression	F3130	

Table 2. Pediatric FDA-approved indications

Schizophrenia	Adolescents (13-17 years)	
Bipolar Mania	Children and Adolescents (10 to 17 years)	Monotherapy

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code. Do not proceed and deny if diagnosis is not listed in Table 1 or Table 2 above (medical appropriateness)	
2. Is the prescription for quetiapine less than or equal to 50 mg/day? (verify days' supply is accurate)	**Yes**: Go to #3	**No:** Trouble-shoot claim processing with the pharmacy.
3. Is planned duration of therapy longer than 90 days?	**Yes:** Go to #4	**No:** Approve for titration up to maintenance dose (60 days).
4. Is reason for dose ≤50 mg/day due to any of the following: • low dose needed due to debilitation from a medical condition or age; • unable to tolerate higher doses; • stable on current dose; or • impaired drug clearance? • any diagnosis in table 1 or 2 above?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny for medical appropriateness. Note: may approve up to 6 months to allow taper.

P&T/DUR Review: *7/18 (DM); 11/17; 9/15; 9/10; 5/10*
Implementation: *TBD; 1/1/18; 10/15; 1/1/11*

Pimavanserin (Nuplazid™) Safety Edit

Goals:

- Promote safe use of pimavanserin in patients with psychosis associated with Parkinson's disease.

Length of Authorization:

- Up to 6 months

Requires PA:

- Pimavanserin

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		
5. What diagnosis is being treated?	Record ICD10 code	
6. Is the treatment for hallucinations and/or delusions associated with Parkinson's disease?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
7. Are the symptoms likely related to a change in the patient's anti-Parkinson's medication regimen?	**Yes:** Go to #4 Consider slowly withdrawing medication which may have triggered psychosis.	**No:** Go to #5
8. Has withdrawal or reduction of the triggering medication resolved symptoms?	**Yes:** Pass to RPh; Deny; medical appropriateness	**No:** Go to #5
9. Is the patient on a concomitant first- or second-generation antipsychotic drug?	**Yes:** Pass to RPh; Deny; medical appropriateness	**No:** Go to #6
10. Has the patient been recently evaluated for a prolonged QTc interval?	**Yes:** Approve for up to 6 months	**No:** Pass to RPh; Deny; medical appropriateness

Risperdal® Consta® Quantity Limit

Goal(s):

- To ensure the use of the appropriate billing quantity. This is a quantity initiative, **not a clinical initiative**. The vial contains 2 mL. The dispensing pharmacy must submit the quantity as 1 vial and not 2 mL.

Length of Authorization:

- Date of service or 12 months, depending on criteria

Requires PA:
Risperdal® Consta®

Approval Criteria		
11. Is the quantity being submitted by the pharmacy expressed correctly as # syringes?	**Yes:** Go to #2	**No:** Have pharmacy correct to number of syringes instead of number of mL.
12. Is the amount requested above 2 syringes per 18 days for one of the following reasons? • Medication lost • Medication dose contaminated • Increase in dose or decrease in dose • Medication stolen • Admission to a long term care facility • Any other reasonable explanation?	**Yes:** Approve for date of service only (use appropriate PA reason)	**No:** Go to #3
13. Is the pharmacy entering the dose correctly and is having to dispense more than 2 syringes per 18 days due to the directions being given on a weekly basis instead of every other week.	**Yes:** Approve for 1 year (use appropriate PA reason)	Note: This medication should NOT be denied for clinical reasons.

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Literature Scan: Pancreatic Enzymes

Date of Review: September 2018

Date of Last Review: September 2017
End Date of Literature Search: 07/03/2018

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

Purpose for Review:
The purpose of this review is to evaluate any new evidence on the use of pancreatic enzymes since the previous literature scan done in 2017.

Research Questions:
1. What is the evidence for comparative efficacy of different pancreatic enzyme preparations for important outcomes (i.e., coefficient of fat absorption)?
2. Is there evidence of differences in harms for the different pancreatic enzyme preparations?
3. Is there evidence of more benefit or harm in different subpopulations who use pancreatic enzymes?

Conclusions:
- There was no new comparative evidence published in the last year on pancreatic enzyme replacement therapy (PERT) that met inclusion criteria for the literature scan as described in current methods. A list of PERT and corresponding indications are listed in **Appendix 3.**

Recommendations:
- Recommend no changes to the preferred drug list (PDL) based on clinical efficacy information.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy
- A literature scan was performed in September 2017 that found no evidence of efficacy or safety differences between the pancreatic enzyme preparations. Overall evidence is of low or insufficient quality and highly dependent on subjective patient records of food diaries. There were no changes to the PDL after executive session, with Creon and Pancrelipase MT 16 being the only preferred products. There are no prior authorization (PA) criteria for this class.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Institute for Clinical and Economic Review (ICER), 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. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated evidence-based clinical practice guidelines.

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:
No new systematic reviews identified.

New Guidelines:
No new guidelines identified.

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

New FDA Safety Alerts:
No safety alerts identified.

Randomized Controlled Trials:
No new randomized controlled trials were identified.

References:

1. Creon Prescribing Information. AbbVie Inc. North Chicago, IL; 2015.
2. Pancreaze® Prescribing Information. Janssen Pharmaceuticals, Inc. Titusville, NJ; 2010.
3. Pancrealipase MT® Prescribing Information. McNeil Consumer & Specialty Pharmaceuticals. Ft. Washington, PA; 2005.
4. Pertyze Prescribing Information. Digestive Care, Inc. Bethlehem, PA; 2017.
5. Ultrace® Prescribing Information. Axcan Scandipharm INC. Birmingham, AL; 2005.
6. Ultresa Prescribing Information. Aptalis Pharma US, Birmingham, AL; 2012.
7. Viokase Prescribing Information. Aptalis Pharma US, Inc. Birmingham, AL; 2012.
8. Zenpep Prescribing Information. Eurand Pharmaceuticals, Inc. Yardley, PA; 2009.

Appendix 1: Current Preferred Drug List

Generic	Brand	FormDesc	PDL
lipase/protease/amylase	CREON	CAPSULE DR	Y
lipase/protease/amylase	PANCRELIPASE MT 16	CAPSULE DR	Y
lipase/protease/amylase	PANCREAZE	CAPSULE DR	N
lipase/protease/amylase	PANCRELIPASE 10000	CAPSULE DR	N
lipase/protease/amylase	PERTZYE	CAPSULE DR	N
lipase/protease/amylase	ULTRASE	CAPSULE DR	N
lipase/protease/amylase	ULTRASE MT 12	CAPSULE DR	N
lipase/protease/amylase	ULTRASE MT 18	CAPSULE DR	N
lipase/protease/amylase	ULTRASE MT 20	CAPSULE DR	N
lipase/protease/amylase	ULTRASE MT 6	CAPSULE DR	N
lipase/protease/amylase	ZENPEP	CAPSULE DR	N
lipase/protease/amylase	PANCRELIPASE	TABLET	N
lipase/protease/amylase	VIOKASE	TABLET	N

Appendix 2: Medline Search Strategy

Database(s): Ovid MEDLINE(R) 1946 to July Week 1 2018

Search Strategy:

#	Searches	Results
1	Pancrelipase/	314
2	creon.mp.	78
3	pertzye.mp.	2
4	ultrase.mp.	2
5	ultrase MT 20.mp.	1
6	ultrase MT 6.mp.	0
7	zenpep.mp.	10
8	viokase.mp. or Pancrelipase/	332
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	372
10	limit 9 to (english language and humans and yr="2017 -Current")	6

Appendix 3: Pancreatic Enzyme Formulations

Table 1. Pancreatic Enzyme Replacement Therapy Products

Name	Type	Indications
Creon®[1]	Delayed release/enteric coated	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis, chronic pancreatitis, pancreatectomy, or other conditions
Pancreaze®[2]	Delayed release/enteric coated	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions
Pancrelipase[3]	Delayed release/enteric coated	Treatment of steatorrhea secondary to pancreatic insufficiency such as cystic fibrosis or chronic alcoholic pancreatitis
Pertyze®[4]	Delayed release/enteric coated	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions
Ultrase®[5]	Delayed release/enteric coated	Indicated for patients with partial or complete exocrine pancreatic insufficiency
Ultresa®[6]	Delayed release/enteric coated	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions
Viokace®[7]	Non-enteric coated	For use in combination with a proton pump inhibitor, is indicated in adults for the treatment of exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatectomy
Zenpep®[8]	Delayed release/enteric coated	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis, or other conditions

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Drug Class Update: Pulmonary Hypertension

Date of Review: September 2018

Date of Last Review: March 2016
Dates of Literature Search: 11/01/2015-06/26/2018

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

Purpose for Class Update: To evaluate new comparative evidence of drug therapy for pulmonary hypertension (PH). PH is classified into 5 specific types. Pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) are the only types of PH with targeted drug therapies and will be the focus of this report.

Research Questions:
1. Are there differences in efficacy or effectiveness of initial monotherapy, initial combination therapy, or sequential combination therapy (i.e., add-on therapy) for treatment of PH based on stage of the disease?
2. Are there differences in the safety profiles of initial monotherapy, initial combination therapy, or sequential combination therapy (i.e., add-on therapy) for treatment of PH?
3. Are there specific subpopulations based on disease severity (World Health Organization [WHO] functional class) or other disease characteristics that may benefit more from a specific drug or combination of drugs?

Conclusions:
- There is no new direct comparative evidence for drug treatment of PAH or CTEPH.
- The American Heart Association and American Thoracic Society guidelines for pediatric pulmonary hypertension were updated in November 2015. Due to limited data available in pediatric patients, primary recommendations were made based on limited populations from single randomized controlled trials (RCTs) or non-randomized studies (level of evidence B). Intravenous or subcutaneous prostanoids or its analogs are recommended for high-risk patients with PAH (Class I, level of evidence B).[1] In low-risk patients, oral PAH-targeted therapy is recommended and should include a phosphodiesterase (PDE)-5 inhibitor or an endothelin receptor antagonists (ERA; Class I, level of evidence B).[1]
- A new formulation of bosentan (Tracleer®), an oral dispersible tablet, was approved by the United States Food and Drug Administration (FDA) in September 2017. Bosentan also received an expanded indication for PAH in pediatric patients at least 3 years of age.
- There have been new safety labeling updates for 8 products since the previous review. Contraindications for riociguat were updated to include idiopathic interstitial pneumonias and more specific language was added surrounding drug interactions with PDE-5 inhibitors. Selexipag labeling was updated to include contraindications with concomitant CYP2C8 inhibitors. Labeling of other products was updated to include more information about adverse effects

for the following: elevated liver enzymes with bosentan, peripheral edema with macitentan, visual loss with PDE-5 inhibitors, and symptomatic hypotension and bleeding risk with injectable and inhaled treprostinil.[2] Monitoring for these adverse effects is recommended.

Recommendations:

- Update prior authorization (PA) criteria to include contraindications for riociguat in patients with idiopathic interstitial pneumonias.
- Evaluate comparative costs in executive session.

Summary of Prior Reviews and Current Policy

There is limited direct comparative evidence evaluating efficacy and safety of treatments for PAH. The majority of available RCTs are placebo-controlled and evaluate changes in functional status or exercise capacity using the 6 minute walking distance (6MWD). Most studies have not been powered to determine differences in morbidity or mortality. Prior reviews suggest that there are no statistically significant differences in clinical worsening (defined as change in WHO functional class, initiation of treatment with intravenous [IV] or subcutaneous [SC] prostanoids, all-cause mortality, heart or lung transplant, or atrial septostomy) between monotherapy treatments for treatment-naïve patients with PAH and WHO functional class II or III.[3] Pooled data based on drug class has suggested that oral phosphodiesterase inhibitors and IV epoprostanil may be associated with a statistically significant mortality reduction compared to placebo.[3] Sequential (add-on) combination therapy may be considered to slow clinical worsening compared to monotherapy. However, there is little data to guide the duration of initial drug therapy before switching or adding another drug.[3] Oral and inhalation therapies have been considered an appropriate option for class II-IV patients but do not necessarily negate the need for IV or SC prostycyclins. Preferred oral formulations include bosentan and sildenafil. Historically, IV epoprostenol had been the treatment of choice in class IV patients based on recommendations from the American College of Chest Physicians and the American College of Cardiology Foundation/American Heart Association and is currently the preferred IV formulation.[3,4]

A PA is currently required for sildenafil to ensure it is used for a funded condition, and clinical PA criteria is required for all non-preferred products listed in **Appendix 1**. Non-preferred products must be prescribed by a pulmonologist or cardiologist. In patients with pulmonary artery hypertension (WHO Group 1), oral therapy may be considered for patients with functional class II-IV symptoms. Riociguat may also be approved for patients with chronic thromboembolic pulmonary hypertension (WHO Group 4) and functional class II-IV symptoms. IV therapy may be approved for patients with pulmonary arterial hypertension (WHO Group 1) and functional class III-IV symptoms.

Background:

Pulmonary hypertension (PH) is defined as a rise in mean pulmonary arterial pressure to greater than 25 mmHg at rest.[5,6] PH is classified into 5 groups: pulmonary arterial hypertension (PAH; World Health Organization [WHO] group 1), PH due to left heart disease (WHO group 2), PH due to lung disease and hypoxia (WHO group 3), chronic thromboembolic pulmonary hypertension (CTEPH, WHO group 4) and PH with an unclear multifactorial cause (WHO group 5).[5,6] Each type of PH has a unique etiology, pathology and management strategy. PAH and CTEPH are the only types of PH with specific targeted drug therapies and will be the focus of this report. Etiology for PAH and CTEPH often includes multiple mechanisms including abnormal function or expression of potassium channels in smooth muscle and abnormal nitric oxide production causing vasoconstriction, endothelial dysfunction, and thrombosis. Hemodynamic changes and vascular remodeling eventually lead to long-term complications such as right ventricular dysfunction, arrhythmias, and ascites. The estimated incidence of adults with PAH is approximately 15-60 cases per 1 million adults.[6] The exact incidence of CTEPH in the US is unclear.[7] In the Oregon Health Plan (OHP) fee-for-service (FFS) population, approximately 700 patient had a diagnosis of primary pulmonary hypertension from 2016-2017. Over the last quarter in 2017, there were approximately 50 OHP FFS patients with claims for PAH-specific medications with the majority of use for preferred drugs.

PAH can also be classified based on the WHO functional status which divides PAH into the following 4 categories: no limitations in physical activity (class I), slight limitations in physical activity (class II), marked limitations in physical activity (class III), and symptoms at rest (class IV).[5,6] Symptoms primarily include respiratory dyspnea, syncope, chest pain, exercise intolerance, and peripheral edema. The estimated 3 year survival is 58-73% with worsening prognosis for patients with higher New York Heart Association (NYHA) functional class, rapidly progressive disease, need for prostanoid therapy, or recurrent hospitalizations.[5] Increased disease severity, impaired exercise capacity, and risk for clinical morbidity or mortality outcomes may also be evaluated using a variety of hemodynamic factors including cardiac index, the 6MWD , oxygen saturation, and right arterial pressure.[1,6]

Current standard of care for patients with PAH (WHO group 1) includes oral calcium channel blockers for patients who respond to acute vasoreactive testing (approximately 10% of patients), diuretics for fluid retention, digoxin to improve cardiac output and slow ventricular rate, and anticoagulants to decrease risk for thromboembolic events.[6] Other supportive care includes oxygen, supervised physical activity, and rehabilitation.[6] PAH-specific therapies may also be considered for patients with functional class II-IV symptoms. Current PAH-specific treatment options include the following drugs:

- PDE-5 inhibitors: sildenafil and tadalafil
- ERAs: bosentan, macitentan, and ambrisentan
- prostacyclin receptor agonists: selexipag
- soluble guanylate cyclase stimulators: riociguat
- prostanoids: epoprostenol, treprostinil, and iloprost

In patients with CTEPH (WHO Group 4), standards of care include supervised cardiopulmonary exercise rehabilitation, supplemental oxygen, diuretics for fluid retention, and lifetime anticoagulants to prevent thromboembolic events. Pulmonary endarterectomy is recommended for surgery-eligible patients, and if successful, may potentially be curative with survival rates of 75-92% at 6 years after surgery.[6,7] However, not all patients are eligible for surgery, and the disease either recurs or is refractory to surgery in 5-35% of cases.[5] Patients who are not surgical candidates may consider drug therapy, primarily treatment with riociguat to improve exercise intolerance. Riociguat is currently the only PAH-specific therapy also FDA-approved for patients with CTEPH. Current guidelines suggest PAH therapies may be considered for off-label use in patients with inoperable CTEPH.[7] However, recommendations are supported by limited evidence such as small RCTs, non-randomized studies, indirect evidence, or lack of clinical outcome data.[7]

Goals of therapy include morbidity and mortality reduction, symptom improvement, and decreased disease progression. Outcomes studied in clinical trials include hemodynamic endpoints, 6MWD, and time to clinical worsening endpoints. The majority of trials have not been designed to evaluate long-term outcomes of mortality or disease progression. 6MWD is often used to evaluate exercise capacity. While worse 6MWD at baseline and rapid decline in 6MWD (>15% over 1 year) may have some prognostic value, improvements in 6MWD have not demonstrated any correlation with mortality reduction or disease progression for patients with PAH.[8] Patients with 6MWD greater than 440 to 500 meters are generally considered to be at low risk for clinical events.[1,6] A minimum clinically important change in 6MWD has not been established and improvements of up to 15% change in 6MWD over 1 year have not been correlated with increased survival compared to patients with no change in 6MWD.[8] Clinical worsening is a composite endpoint often defined as time to change in WHO functional class, initiation of treatment with IV or SC prostanoids, all-cause mortality, heart or lung transplant, or atrial septostomy.[9]

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), the Cochrane Collaboration, National Institute for

Health and Clinical Excellence (NICE), Department of Veterans Affairs, Institute for Clinical and Economic Review (ICER), 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:

A Cochrane review examining the efficacy of riociguat for PH was published in 2016.[5] Five RCTs (n=966) were included in the review and only 3 had data suitable for a pooled analysis.[5] Included studies had low risk of selection bias and unclear performance and detection bias. Attrition bias was low for 3 included studies and all trials were sponsored by the drug manufacturer.[5] Exercise capacity as evaluated by mean change in the 6MWD for patients with PH was 30.13 meters (95% CI 5.29 to 54.96) compared to placebo with significant heterogeneity (I^2=64%).[5] There was no statistical difference between riociguat and placebo for outcomes of mortality (OR 0.57, 95% CI 0.18 to 1.80), change in WHO functional class (OR 1.53, 95% CI 0.87 to 2.72), time to clinical worsening (OR 0.45, 95% CI 0.17 to 1.14), or serious adverse events (OR 1.12, 95% CI 00.66 to 1.90).[5] Subgroup analyses were evaluated based on type of PH. Two studies evaluated outcomes for PAH and a single study evaluated patients with CTEPH. In patients with CTEPH, compared to placebo riociguat had a statistical significant difference for improvement in WHO functional class (33% vs. 15%; OR 2.80, 95% CI 1.43 to 5.46) and exercise capacity (45 m, 95% CI 23.87 to 66.12) but not mortality, clinical worsening, or serious adverse events.[5] In patients with PAH, clinical worsening was statistically better than placebo (1.2% vs. 6.4%, OR 0.18, 95% CI 0.05 to 0.68), but outcomes of mortality, exercise capacity, change in WHO functional status, and serious adverse events were not statistically different.[5]

After review, 9 systematic reviews were excluded due to poor methodological quality, wrong study design of included trials (e.g., observational), analytical methods (e.g., network meta-analyses), comparator (e.g., no control), population (non-United States), setting (inpatient), or outcome studied (e.g., non-clinical).

New Guidelines:

Guidelines Which Met Quality Standards:

American Heart Association and American Thoracic Society

The American Heart Association and American Thoracic Society guidelines for pediatric pulmonary hypertension were updated in November 2015.[1] The guideline committee acknowledged that data in children was lacking or was often based on observational studies or extrapolated from experience in adults.[1] The majority of pharmacologic recommendations were either made based on limited populations from single RCTs or non-randomized studies (level of evidence B) or consensus opinion, case studies, or standard of care (level of evidence C).[1] Of the guideline and writing committee, 11 of the 27 members disclosed funding from pharmaceutical manufacturers for research grants, speaking honoraria, or consulting.[1] Four members had funding which was considered "significant" defined as greater than $10,000 or more than 5% of the individual's gross income.[1]

Recommendations were made for patients considered low-risk and high-risk based on disease severity. Patients were considered high-risk if they had clinical evidence of right ventricular failure, pericardial effusion, WHO Class III-IV, recurrent syncope, significantly elevated BNP, 6MWD less than 300 meters, peak volume of oxygen during cardiopulmonary testing less than 15 mL/kg/min, or hemodynamics indicating severe disease.[1] Intravenous or subcutaneous prostacyclin or its analogs are recommended for high-risk patients (Class I, level of evidence B).[1] In low-risk patients, oral PAH-targeted therapy is recommended and should include a phosphodiesterase inhibitor or an ERA (Class I, level of evidence B).[1] Oral phosphodiesterase inhibitors may also be considered during

inhaled nitric oxide withdrawal.[1] Switching from parenteral to oral/inhaled therapy may be considered for patients with sustained and near-normal pulmonary hemodynamics (Class IIB, level of evidence C).[1] Close monitoring by an experienced pediatric pulmonary hypertension center is recommended upon switching to oral or inhaled therapy. Combination therapy may be considered to achieve therapeutic targets (Class IIa, level of evidence C).[1]

After review, 3 guidelines were excluded due to poor quality.[6,10]

New Formulations or Indications:
A new formulation of bosentan (Tracleer®), an oral dispersible tablet, was approved by the FDA in September 2017. The new formulation is FDA-approved for treatment of PAH in adults and pediatric patients at least 3 years of age.[11] Bosentan oral tablets had previously only been approved for adults with PAH. The expanded indication to pediatric patients was based on efficacy data from an open-label, uncontrolled trial of 19 pediatric patients with WHO functional class II or III.[11] Safety data included 100 pediatric patients treated for a median of 17 months.[11] Hemodynamic improvements including peripheral vascular resistance were similar to parameters observed in adults.[11]

New FDA Safety Alerts:

Table 1. Description of new FDA Safety Alerts[2]

Generic Name	Brand Name	Month/Year of Change	Location of Change	Addition or Change and Mitigation Principles (if applicable)
Bosentan	Tracleer®	09/2017	Warnings/Precautions	In a pooled analysis of pediatric studies, 2% of patients have elevations in liver aminotransferases >3 times the upper limit of normal (ULN). Avoid initiation of treatment with elevated liver enzymes (>3x ULN). In patients with WHO functional class II, consider whether benefits of treatment outweigh risks of hepatotoxicity. Information regarding embryo-fetal toxicity based on data from animal reproduction studies was added to the labeling. Bosentan is contraindicated in pregnancy and is only available through a REMS program.
Macitentan	Opsumit®	03/2017	Warnings/Precautions	Warnings including peripheral edema and fluid retention were added to product labeling. Patients with concomitant left ventricular dysfunction may be at increased risk for fluid retention and heart failure exacerbations. Monitoring is recommended with treatment discontinuation if clinically appropriate.
Riociguat	Adempas®	01/2017	Contraindications	Riociguat is contraindicated in patients with PAH associated with idiopathic interstitial pneumonias. Labeling also updated to include the following information on drug interactions: avoid riociguat administration within 24 hours of sildenafil use or within 24 hours before or 48 hours after tadalafil use.

Selexipag	Uptravi®	07/2017	Contraindications	Labeling was updated to include contraindications with concomitant use of strong CYP2C8 inhibitors (eg, gemfibrozil).
Sildenafil Tadalafil	Revatio® Adcirca®	07/2017 05/2017	Warnings/Precautions	Labeling was updated to include information concerning visual loss and non-arteritic anterior ischemic optic neuropathy based on information from 2 observational studies. Results indicate a 2-fold increase of optic events upon initiation of a phosphodiesterase inhibitor compared to estimated risk prior to treatment. Estimated annual incidence of non-arteritic anterior ischemic optic neuropathy is 2-12 cases per 100,000 in males greater than 50 years of age.
Treprostinil	Remodulin® Tyvaso®	06/2018 06/2016	Warnings/Precautions	Labeling for Remodulin® was updated to include warnings for symptomatic hypotension and risk of bleeding due to platelet aggregation. Labeling for Tyvaso® was also updated to include risk for bleeding.

Randomized Controlled Trials:

A total of 146 citations were manually reviewed from the initial literature search. After further review, 145 citations were excluded because of wrong study design (eg, observational or post-hoc analyses), setting (inpatient), comparator (eg, no control), or outcome studied (eg, non-clinical). The remaining 1 trial is summarized in the table below. The full abstract is included in **Appendix 2**.

Table 2. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Vizza, et al. 2017.[12] MC, DB, PC RCT N=103	1. Sildenafil 20 mg three times daily 2. Placebo Patients were on stable bosentan therapy for at least 3 months (62.5 or 125 mg BID)	Idiopathic PAH with connective tissue disease	Change in 6-minute walk distance at 12 weeks	Mean change from baseline 1. 13.6 m 2. 14.1 m LSMD -2.4 m (90% CI -21.8 to 17.1 m); p=0.6

Abbreviations: BID = twice daily; DB = double blind; LSMD = least squares mean difference; MC = multicenter; PAH = pulmonary arterial hypertension; PC = placebo controlled; RCT = randomized clinical trial; SD = standard deviation, etc.

References:

1. Abman SH, Hansmann G, Archer SL, et al. Pediatric Pulmonary Hypertension: Guidelines From the American Heart Association and American Thoracic Society. *Circulation.* 2015;132(21):2037-2099.
2. Food and Drug Administration. Drug Safety Labeling Changes (SLC). https://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/. Accessed June 26, 2018.
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Appendix 1: Current Preferred Drug List

PAH Oral and Inhaled Drugs

Generic	Brand	FormDesc	Route	PDL
bosentan	TRACLEER	TABLET	ORAL	Y
sildenafil citrate	REVATIO	TABLET	ORAL	Y
sildenafil citrate	SILDENAFIL	TABLET	ORAL	Y
ambrisentan	LETAIRIS	TABLET	ORAL	N
bosentan	TRACLEER	TAB SUSP	ORAL	N
iloprost tromethamine	VENTAVIS	AMPUL-NEB	INHALATION	N
macitentan	OPSUMIT	TABLET	ORAL	N
riociguat	ADEMPAS	TABLET	ORAL	N
selexipag	UPTRAVI	TAB DS PK	ORAL	N
selexipag	UPTRAVI	TABLET	ORAL	N
sildenafil citrate	REVATIO	SUSP RECON	ORAL	N
sildenafil citrate	SILDENAFIL CITRATE	TABLET	ORAL	N
sildenafil citrate	VIAGRA	TABLET	ORAL	N
tadalafil	ADCIRCA	TABLET	ORAL	N
treprostinil	TYVASO	AMPUL-NEB	INHALATION	N
treprostinil diolamine	ORENITRAM ER	TABLET ER	ORAL	N
treprostinil/neb accessories	TYVASO REFILL KIT	AMPUL-NEB	INHALATION	N
treprostinil/nebulizer/accesor	TYVASO INSTITUTIONAL START KIT	AMPUL-NEB	INHALATION	N
treprostinil/nebulizer/accesor	TYVASO STARTER KIT	AMPUL-NEB	INHALATION	N

PAH Parenteral Drugs

Generic	Brand	FormDesc	Route	PDL
epoprostenol sodium (glycine)	EPOPROSTENOL SODIUM	VIAL	INTRAVEN	Y
epoprostenol sodium (glycine)	FLOLAN	VIAL	INTRAVEN	Y
epoprostenol sodium (arginine)	VELETRI	VIAL	INTRAVEN	N
sildenafil citrate	REVATIO	VIAL	INTRAVEN	N
sildenafil citrate	SILDENAFIL CITRATE	VIAL	INTRAVEN	N
treprostinil sodium	REMODULIN	VIAL	INJECTION	N

Appendix 2: Abstracts of Comparative Clinical Trials

Vizza CD, Jansa P, Teal S, Dombi T, Zhou D. Sildenafil dosed concomitantly with bosentan for adult pulmonary arterial hypertension in a randomized controlled trial. BMC cardiovascular disorders. 2017;17(1):239.

BACKGROUND: Few controlled clinical trials exist to support oral combination therapy in pulmonary arterial hypertension (PAH). METHODS: Patients with PAH (idiopathic [IPAH] or associated with connective tissue disease [APAH-CTD]) taking bosentan (62.5 or 125 mg twice daily at a stable dose for >=3 months) were randomized (1:1) to sildenafil (20 mg, 3 times daily; n = 50) or placebo (n = 53). The primary endpoint was change from baseline in 6-min walk distance (6MWD) at week 12, assessed using analysis of covariance. Patients could continue in a 52-week extension study. An analysis of covariance main-effects model was used, which included categorical terms for treatment, baseline 6MWD (<325 m; >=325 m), and baseline aetiology; sensitivity analyses were subsequently performed. RESULTS: In sildenafil versus placebo arms, week-12 6MWD increases were similar (least squares mean difference [sildenafil-placebo], -2.4 m [90% CI: -21.8 to 17.1 m]; P = 0.6); mean +/- SD changes from baseline were 26.4 +/- 45.7 versus 11.8 +/- 57.4 m, respectively, in IPAH (65% of population) and -18.3 +/- 82.0 versus 17.5 +/- 59.1 m in APAH-CTD (35% of population). One-year survival was 96%; patients maintained modest 6MWD improvements. Changes in WHO functional class and Borg dyspnoea score and incidence of clinical worsening did not differ. Headache, diarrhoea, and flushing were more common with sildenafil. CONCLUSIONS: Sildenafil, in addition to stable (>=3 months) bosentan therapy, had no benefit over placebo for 12-week change from baseline in 6MWD. The influence of PAH aetiology warrants future study. TRIAL REGISTRATION: ClinicalTrials.gov NCT00323297 (registration date: May 5, 2006).

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to June 20, 2018

1	exp Hypertension, Pulmonary/	32511
2	exp Endothelin Receptor Antagonists/	4694
3	bosentan.mp.	2459
4	exp Sildenafil Citrate/	4975
5	ambrisentan.mp.	345
6	exp Tadalafil/	1206
7	exp Phosphodiesterase 5 Inhibitors/	7335
8	exp prostaglandins/ or exp prostaglandins i/ or exp epoprostenol/ or exp prostaglandins, synthetic/ or exp iloprost/	97655
9	macitentan.mp.	211
10	treprostinil.mp.	485
11	selexipag.mp.	91
12	riociguat.mp.	248
13	exp Guanylate Cyclase-Activating Proteins/	223
14	guanylate cyclase/ or exp soluble guanylyl cyclase/	7123
15	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	117224
16	1 and 15	4091
17	limit 16 to (english language and humans)	3019
18	limit 17 to yr="2015 -Current"	476
19	limit 18 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)	146

Appendix 4: Key Inclusion Criteria

Population	Patients with pulmonary artery hypertension (United States population)
Intervention	Drugs listed in **Appendix 1**
Comparator	Active or placebo comparisons of drugs listed in **Appendix 1**.
Outcomes	1) Mortality 2) Hospitalizations 3) Heart or lung transplant 4) Atrial septostomy 5) Change in WHO functional class or functional status 6) Exercise capacity
Timing	Any study duration; literature search from 11/01/2015 to 06/26/2018
Setting	Outpatient

Oral/Inhaled Pulmonary Arterial Hypertension Agents

Goals:

- Restrict use to appropriate patients with pulmonary arterial hypertension (PAH) or chronic thromboembolic pulmonary hypertension and World Health Organization (WHO) Functional Class II-IV symptoms.
- Restrict use to conditions funded by the Oregon Health Plan (OHP). Note: erectile dysfunction is not funded by the OHP.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred drugs

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an OHP-funded diagnosis?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Is the drug being prescribed by a pulmonologist or cardiologist?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.
4. Is there a diagnosis of pulmonary arterial hypertension (PAH) (WHO Group 1; ICD10 I27.0)?	**Yes:** Go to #~~8~~9	**No:** Go to #5
5. Is there a diagnosis of chronic thromboembolic pulmonary hypertension (WHO Group 4; ICD10 I27.24)?	**Yes:** Go to #6	**No:** Go to #1~~0~~
6. Is the request for riociguat (Adempas®)?	**Yes:** Go to #7	**No:** Go to #1~~0~~
7. Is there documentation that the patient has a medical history of PAH associated with idiopathic interstitial pneumonias?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #8

Approval Criteria		
8. Is the patient classified as having World Health Organization (WHO) Functional Class II-IV symptoms?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
9. Will the prescriber consider a change to a preferred product? Note: preferred products do not require PA.	**Yes:** Inform prescriber of preferred alternatives in class.	**No:** Go to #10~~9~~
10. Is the patient classified as having World Health Organization (WHO) Functional Class II-IV symptoms?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
11. RPh Only: Prescriber must provide supporting literature for use.	**Yes:** Approve for length of treatment.	**No:** Deny; not funded by the OHP

P&T Review: *9/18 (SS); 3/16; 7/14; 3/14; 2/12; 9/10*
Implementation: *TBD; 10/13/16; 5/1/16; 5/14/12; 1/24/12; 1/1/11*

Injectable Pulmonary Arterial Hypertension Agents (IV/SC)

Goals:

- Restrict use to patients with pulmonary arterial hypertension (PAH) and World Health Organization (WHO) Functional Class III-IV symptoms.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred drugs (pharmacy and physician administered claims)

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis an OHP-funded condition?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Will the prescriber consider a change to a preferred product? Note: preferred products do not require PA.	**Yes:** Inform prescriber of preferred alternatives in class.	**No:** Go to #4
4. Is there a diagnosis of pulmonary arterial hypertension (PAH) (WHO Group 1; ICD 10 I27.0)? Note: injectable PAH medications are not FDA-approved for other forms of pulmonary hypertension.	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Is the patient classified as having World Health Organization (WHO) Functional Class III-IV symptoms?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
6. Is the drug being prescribed by a pulmonologist or a cardiologist?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness.

P&T Review: 9/18 (SS); 3/16; 9/12
Implementation: 10/13/16; 1/1/13

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Drug Class Literature Scan: Attention Deficit Hyperactivity Disorder

Date of Review: September 2018

Date of Last Review: September 2017
Literature Search: 06/30/17 – 06/08/18

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

Conclusions:
- This literature scan identified 4 systematic reviews[1-4], 1 guideline[5], 1 new formulation (Adzenys ER™)[6], 1 United States Food and Drug Administration (FDA) safety update (rebound hypertension in guanfacine ER)[7], and 1 retrospective safety study[8]. The identified literature supports current policy for attention deficit hyperactivity disorder (ADHD) drugs.
- An Agency for Healthcare Research and Quality (AHRQ) review on ADHD treatment in children and adolescents found insufficient comparative evidence for all efficacy and safety outcomes except for gastrointestinal side effects (slightly higher with atomoxetine compared with methylphenidate; low strength of evidence).[4]
- A Cochrane systematic review on nonrandomized studies of methylphenidate for ADHD in children and adolescents found an increased risk of serious adverse events compared to no intervention (risk ratio 1.36; 95% confidence interval [CI] 1.17 to 1.57).[1]
- An update to the National Institute for Health and Care Excellence (NICE) guideline on ADHD diagnosis and management recommends methylphenidate as a first-line pharmacologic treatment option for both adults and children.[5] Lisdexamfetamine is also a first-line pharmacologic option for adults and a second-line option for children.[5]
- No significant trends were noted in diagnoses of ADHD, narcolepsy, or substance abuse/dependence for Oregon Health Plan (OHP) Fee-for-Service (FFS) patients prescribed ADHD medications listed in **Appendix 1**.

Recommendations:
- No further review or research needed.
- Update guanfacine extended-release dosing in Table 2 of the prior authorization criteria (**Appendix 6**) to clarify FDA-recommended maximum daily doses for monotherapy versus adjunctive therapy.
- Evaluate comparative costs in executive session.

Summary of Prior Reviews and Current Policy
Evidence summarized in prior reviews has demonstrated that compared to placebo, stimulants and non-stimulant medications have benefit for patients with ADHD. However, no consistent differences have been demonstrated between different formulations (immediate release [IR] vs. extended release [ER]) in this class of drugs. Additionally, there is insufficient evidence that directly compares general effectiveness outcomes for different drugs for ADHD in children or

adults.[9,10] The most common adverse effects from stimulants are appetite loss, abdominal pain, headaches and sleep disturbance; only low quality evidence suggests any differences in harms between the agents.[9]

In the Oregon Health Plan (OHP) Fee-for-Service (FFS) population, all medications in the ADHD class have age and quantity safety limits which ensure they are being used in the appropriate age range and within safe dosing parameters. If the request is for a non-preferred agent or any agent exceeding the age or quantity limits, a safety edit ensures that medication use is consistent with current best practices and also promotes care by a psychiatrist for patients requiring therapy outside of best-practice guidelines. Preferred medications in this class include atomoxetine, dexmethylphenidate, dextroamphetamine/amphetamine, lisdexamfetamine dimesylate, and methylphenidate. This class of the OHP FFS Preferred Drug List (PDL) contains three mental health carve-out medications: atomoxetine, clonidine, and guanfacine. These three medications are exempt from traditional PDL and prior authorization (PA) requirements. However, clinical PA criteria which address safety concerns or medically inappropriate use may be implemented.

OHP FFS Utilization Summary

In the OHP FFS population during the second quarter of 2018, utilization of preferred, voluntary, and non-preferred agents in this class was 48%, 48%, and 4%, respectively.

At the time of a recent OHP FFS drug use evaluation (DUE) completed in July 2016, it was recommended to continue to monitor use of ADHD medications in the adult populations and to evaluate trends in adults.[11]

An analysis of patients with a paid FFS claim for at least one medication in the ADHD class from 7/1/2017 to 6/30/2018 and their associated medical diagnoses was completed to evaluate for medically appropriate use. Patients included in the analysis had at least 75% OHP eligibility in the year prior to the first ADHD claim and the presence of diagnoses were evaluated in the year prior to the first ADHD claim. Diagnoses of ADHD and narcolepsy were specifically searched due to their FDA-approved indications in the drugs of the ADHD class. Additionally, substance abuse, substance dependence, and poisoning diagnoses were searched due to safety concerns. Results for this query are outlined in **Table 1**.

Table 1. OHP FFS Utilization of ADHD Drugs by Selected Diagnoses

Patient Age	Diagnosis	ICD-10 codes	Number of unique patients with a paid FFS claim for ≥1 medication in the ADHD class	Percent of patients based on total in age group
Patients <18 years			**7,161**	
	ADHD	F90.x	5,589	78.0%
	Narcolepsy	G47.41, G47.411, G47.419, G47.42, G47.421, or G47.429	2	0.0%
	No diagnosis of ADHD or narcolepsy	Absence of F90.x AND absence of G47.41, G47.411, G47.419, G47.42, G47.421, and G47.429	1,571	21.9%
	Substance abuse or dependence (including alcohol, opioid, cocaine, cannabis, other stimulant, other psychoactive substance, or non-psychoactive substances)	F10.1x, F10.2x, F15.1x, F15.2x, F11.1x, F11.2x, F19.1x, F19.2x, F12.1x, F12.2x, F14.1x, F14.2x, or F55.x	185	2.6%

	Poisoning by unspecified psychostimulants, amphetamines, methylphenidate, or other psychostimulants (accidental [unintentional], intentional self-harm, or undetermined)	T43.601x, T43.602x, T43.604x, T43.621x, T43.622x, T43.624x, T43.631x, T43.632x, T43.634x, T43.691x, T43.692x, or T43.694x	13	0.2%
Patients ≥18 years			**3,439**	
	ADHD	F90.x	2,197	63.9%
	Narcolepsy	G47.41, G47.411, G47.419, G47.42, G47.421, or G47.429	15	0.4%
	No diagnosis of ADHD or narcolepsy	Absence of F90.x AND absence of G47.41, G47.411, G47.419, G47.42, G47.421, and G47.429	1,232	35.8%
	Substance abuse or dependence (including alcohol, opioid, cocaine, cannabis, other stimulant, other psychoactive substance, or non-psychoactive substances)	F10.1x, F10.2x, F15.1x, F15.2x, F11.1x, F11.2x, F19.1x, F19.2x, F12.1x, F12.2x, F14.1x, F14.2x, or F55.x	985	28.6%
	Poisoning by unspecified psychostimulants, amphetamines, methylphenidate, or other psychostimulants (accidental [unintentional], intentional self-harm, or undetermined)	T43.601x, T43.602x, T43.604x, T43.621x, T43.622x, T43.624x, T43.631x, T43.632x, T43.634x, T43.691x, T43.692x, or T43.694x	17	0.5%

Compared to the DUE completed in July 2016, this data shows slightly higher proportions of patients in both pediatric (78.0% vs. 63.9%, respectively) and adult (63.9% vs. 55.7%, respectively) groups with a diagnosis of ADHD.[11] There are also slightly lower proportions of patients with a diagnosis of substance abuse or dependence who have a paid claim for a medication in the ADHD class in this data compared to the 2016 DUE in children (2.6% vs. 4.4%, respectively) and adult (28.6% vs. 33.4%, respectively).[11] A small percentage of patients also had a diagnosis of poisoning by stimulants; this data was not evaluated in the 2016 DUE and was instead evaluated by ED visits and hospitalization counts.

As a full analysis similar to the previous DUE was not completed, there may be differences in populations which may impact these results. Claims data may also be limited by incomplete reporting of diagnoses. Furthermore, differences between the ICD-9 codes utilized in the DUE and the ICD-10 codes in this analysis may impact results.

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, BMJ Clinical Evidence, 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. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

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:

Agency for Healthcare Research and Quality: ADHD Diagnosis and Treatment in Children and Adolescents

In January 2018, AHRQ published a comparative effectiveness review on ADHD diagnosis and treatment in children and adolescents as a targeted update to a 2011 AHRQ systematic review.[4] Trials published between January 1, 2009 and November 7, 2016 of children 17 years of age and younger with any pharmacologic treatment of ADHD, alone or in combination, were included.[4] The focus of this summary is on evidence from high quality trials or outcomes with high to moderate quality evidence. Trials reporting only placebo comparisons, and comparisons to non-pharmacologic treatments are excluded from this summary.[4]

For comparative pharmacologic efficacy evidence, only one fair quality trial was identified.[4] This trial compared atomoxetine versus osmotic release oral system methylphenidate and found no difference at 6 months in the proportion of patients achieving at least a 40% reduction from baseline in the Conners Comprehensive Behavior Rating Scale-Teacher hyperactive, inattentive, and behavior subscales (insufficient strength of evidence).[4] Other identified trials were of poor quality.[4] For safety outcomes, there was low strength of evidence that the proportion of patients reporting gastrointestinal side effects was slightly higher with atomoxetine compared with methylphenidate (3 observational studies; n=1,966).[4] Other findings related to safety outcomes were all insufficient strength of evidence and are listed below in **Table 2**.

The report concluded that there was limited comparative pharmacologic evidence since the time of the initial report in 2011 and insufficient evidence for all comparative pharmacologic efficacy and safety outcomes except for gastrointestinal effects.[4]

Table 2. AHRQ Comparative Pharmacologic Clinical Safety Outcomes Findings[4]

Outcome	Comparators	Quality of Trial(s)	Result	Strength of Evidence
Gastrointestinal AEs	Atomoxetine vs. methylphenidate	Fair to good	Higher incidence with atomoxetine*: Rate ratio 4.56; 95% CI 2.0 to 10.43	Low
Adverse reactions	Atomoxetine vs. methylphenidate	Fair to good	Higher incidence with atomoxetine*: Relative risk 3.57; 95% CI 1.92 to 6.64	Insufficient
Cardiovascular AEs	Atomoxetine vs. methylphenidate	Fair to good	Higher incidence with atomoxetine*: Rate ratio 3.43; 95% CI 1.21 to 9.76	Insufficient
Neuropsychiatric AEs	Atomoxetine vs. methylphenidate	Fair to good	Higher incidence with atomoxetine*: Rate ratio 2.54; 95% CI 1.34 to 4.74	Insufficient

Abbreviations: AE = adverse event; CI = confidence interval; ER = extended-release; IR = immediate-release

*Absolute rates not reported

Cochrane Collaboration: Adverse Events in Non-Randomized Studies of Methylphenidate

In May 2018, the Cochrane Collaboration published a systematic review of adverse events in non-randomized, observational studies (n=260 studies) of methylphenidate for ADHD in children and adolescents.[1] The primary outcomes were serious adverse events, withdrawal of methylphenidate due to serious adverse events, and withdrawal of methylphenidate due to adverse events of unknown severity.[1] Patients ranged from 3 to 20 years of age and were predominantly

male.[1] Risk of bias ranged from moderate to critical in the studies (primarily due to their non-randomized design) and the GRADE quality rating of the evidence was insufficient for all outcomes.[1] However, this information may still be beneficial to assist providers in evaluating risks versus benefits of therapy. In comparative studies, methylphenidate had a higher incidence of serious adverse events compared to no intervention (risk ratio 1.36; 95% CI 1.17 to 1.57; 2 studies, n=72,005).[1] In non-comparative cohort studies, 1.2% of methylphenidate-treated patients experienced a serious adverse event (95% CI 0.70% to 2.00%; 51 studies, n=162,422).[1] Withdrawal from methylphenidate due to any serious event was also 1.2% (95% CI 0.60% to 2.30%; 7 studies, n=1,173) and withdrawal due to adverse events of unknown severity occurred in 7.30% of patients (95% CI 5.30% to 10.0%; 22 studies; n=3,708).[1] Also in non-comparative cohort studies, 51.2% of patients treated with methylphenidate experienced a non-serious adverse event (95% CI 41.2% to 61.1%; 49 studies; n=13,978), 6.20% of patients discontinued methylphenidate due to non-serious adverse events (95% CI 4.80% to 7.90%; 37 studies; n=7,142), and 16.2% of patients withdrew from the study for unknown reasons (95% CI 13.0% to 19.9%; 57 studies; n=8,340).[1] The specific types of serious adverse events experienced were not described, but frequently reported categories of serious adverse events included central nervous system, cardiovascular, and respiratory system events.[1] The authors concluded that methylphenidate may be associated with a number of serious adverse events and monitoring adverse events is of high importance.[1]

Canadian Agency for Drugs and Technologies in Health: Guanfacine HCl ER for ADHD

In March 2018, CADTH published a rapid response report on guanfacine hydrochloride extended-release for ADHD.[2] Efficacy results focused on low quality indirect network meta-analyses and one poor quality RCT.[2,12] Therefore, efficacy results will not be discussed. Direct comparative safety evidence was limited to guanfacine extended-release (ER) versus placebo which came from four systematic reviews of RCT data.[2] Discontinuations due to treatment-emergent adverse events was significantly greater in the guanfacine ER groups compared to placebo (odds ratio [OR] range: 2.94-4.49; 3 meta-analyses; absolute numbers not reported).[2] Abdominal pain and fatigue were also significantly greater with guanfacine ER compared to placebo (abdominal pain: OR 2.04, 95% CI 1.37 to 3.13; fatigue: OR 2.70, 95% CI 1.89 to 3.85; 3 meta-analyses; absolute numbers not reported).[2]

Canadian Agency for Drugs and Technologies in Health: Clonidine for Psychiatric Conditions and Symptoms

In February 2018, CADTH published a rapid response report on clonidine for the treatment of psychiatric conditions and symptoms.[3] One randomized controlled trial and 3 non-randomized studies (2 retrospective chart reviews; 1 retrospective post-hoc analysis cohort study) provided clinical evidence for the report.[3] Retrospective analyses and poor quality RCT efficacy data will not be discussed due to the low quality of evidence.[3,13] In regards to harms, one retrospective chart review (quality not graded by CADTH; limited by analysis not adjusting for confounders) evaluated potential misuse and abuse of clonidine and found that harms associated with clonidine overdose include impaired consciousness, miosis, hypothermia, bradycardia, hypotension, and severe hypertension.[3] Frequency of clonidine overdose overall was not reported.[3]

After review, 1 systematic review was excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[14]

New Guidelines:

National Institute for Health and Care Excellence

In March 2018, NICE published an update to their 2008 guideline on ADHD diagnosis and management.[5] In this update, new recommendations were made for medication treatment, review of medication, and discontinuation, among other topics.[5] Selected recommendations regarding pharmacologic treatment are reported below. This guidance is limited in that several medications in the ADHD class, including dexmethylphenidate, dextroamphetamine/amphetamine, methamphetamine, and amphetamine were not included in the literature search for the evidence as they are not licensed for the treatment in ADHD in the United Kingdom.[15]

Medication Choice:

Recommendations based on costs in the United Kingdom are excluded from the summary below.

- Children aged 5 years and over and young people:
  - Offer methylphenidate (either short or long acting) as the first-line pharmacological treatment.[5]
  - Consider switching to lisdexamfetamine in patients who have had a 6 week methylphenidate trial and have not derived enough benefit in ADHD symptoms and associated impairment.[5]
  - Offer atomoxetine or guanfacine if patients cannot tolerate methylphenidate or lisdexamfetamine or their symptoms have not responded to separate 6 week trials of lisdexamfetamine and methylphenidate, having considered alternative preparations and adequate doses.[5]
- Adults:
  - Lisdexamfetamine or methylphenidate are recommended as first-line pharmacological treatment options. Trials of each medication are recommended if the patient has not derived enough benefit in ADHD symptoms and associated impairment from one of the medications.[5]
  - Offer atomoxetine if patients cannot tolerate lisdexamfetamine or methylphenidate or their symptoms have not responded to separate 6 week trials of lisdexamfetamine and methylphenidate, having considered alternative preparations and adequate doses.[5]
- Further medication choices:
  - Obtain second opinion or refer to tertiary service if ADHD symptoms are unresponsive to one or more stimulants and one non-stimulant.[5]
  - Do not offer the following medications without advice from tertiary ADHD service:
    - Guanfacine: for adults[5]
    - Clonidine: for children with ADHD and sleep disturbance, rages or tics[5]
    - Atypical antipsychotics in addition to stimulants: for patients with ADHD and coexisting pervasive aggression, rage or irritability[5]
    - Medications not listed in the previously described recommendations[5]
- Patients with coexisting conditions:
  - Offer the same medication choices to patients with ADHD and anxiety disorder, tic disorder or autism spectrum disorder as other patients with ADHD.[5]
  - For patients experiencing an acute psychotic or manic episode: stop any ADHD medication and consider restarting or starting new ADHD medication after the episode has resolved.[5]

Considerations When Prescribing ADHD Medication:

- Modified-release once daily preparation considerations: convenience, improving adherence, reducing stigma (reduced need for doses during school or work), reducing problems of storing and administering controlled drugs at school, the risk of stimulant misuse and diversion with immediate-release preparations, and pharmacokinetic profiles.[5]
- Immediate-release and modified-release preparations combinations may be used to optimize effect.[5]
- Be cautious about prescribing stimulants for ADHD if there is a risk of diversion for cognitive enhancement or appetite suppression.[5]
- Do not offer immediate or modified-release stimulants that can be easily injected or insufflated if there is a risk of stimulant misuse.[5]

Monitoring and Discontinuation

- Monitor effectiveness of medication and adverse effects.[5]

- Depending on age and other patient characteristics, monitoring may include: height and weight, cardiovascular, tics, sexual dysfunction, seizures, sleep, worsening behavior, and stimulant diversion.[5]
- ADHD medication should be reviewed at least once a year to discuss with the patient whether the medication should be discontinued.[5]
- Consider trial periods of stopping medication or reducing the dose when assessment of the overall balance of benefits and harms suggests this may be appropriate.[5]

New Formulations:

In September 2017, a new formulation of amphetamine extended-release oral suspension (Adzenys ER™) was approved by the FDA for the treatment of ADHD in patients 6 years and older.[6] This formulation was approved based on studies of mixed salts of a single-entity amphetamine product extended-release capsules (MAS ER) for the treatment of ADHD.[6] No clinical trials specific to this new formulation were completed and MAS ER study details on results were not reported in depth in the FDA package labeling. The first MAS ER study included pediatric patients age 6-12 years with ADHD.[6] Patients received 10, 20, or 30 mg of the MAS ER capsules or placebo once daily in the morning for three weeks.[6] The primary outcome was the Attention Deficit Hyperactivity Disorder-Rating Scale IV (ADHD-RS-IV; 18 item symptom scale) total score, and patients who received MAS ER showed statistically significant improvements in this outcome for both morning and afternoon assessments compared to patients taking placebo.[6] In a classroom analogue study, pediatric patients showed statistically significant improvements on the teacher-rated Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) scale Attention and Deportment variables as well as the Permanent Product Measure of Performance (PERMP) scale compared to those treated with placebo.[6] In a third pediatric study, patients age 13-17 years showed statistically significantly greater improvements with MAS ER 10 mg, 20 mg, 30 mg, and 40 mg, compared to those treated with placebo.[6] However, there was inadequate evidence that doses greater than 20 mg/day provided additional benefit.[6] One study was also completed in adults receiving 20, 40, or 60 mg of MAS ER or placebo once daily for four weeks.[6] Improvements in the ADHD-RS were seen for all MAS ER doses but doses over 20 mg/day did not provide additional benefit.[6]

New FDA Safety Alerts:

Table 3. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Guanfacine extended-release[7]	Intuniv®	11/2017	Warnings and Precautions	In post marketing experience, abrupt discontinuation has resulted in clinically significant and persistent rebound hypertension above baseline levels and increases in heart rate.[7] To minimize risk of rebound hypertension upon discontinuation, total daily dose should be tapered in increments of no more than 1 mg every 3-7 days.[7] Blood pressure and heart rate should be monitored when reducing the dose or discontinuing.[7]

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Appendix 1: Current Preferred Drug List

Route	Formulation	Brand	Generic	PDL	Carveout
ORAL	TABLET	METHYLPHENIDATE HCL	methylphenidate HCl	Y	
ORAL	TABLET	RITALIN	methylphenidate HCl	Y	
ORAL	CPBP 30-70	METADATE CD	methylphenidate HCl	Y	
ORAL	CPBP 30-70	METHYLPHENIDATE HCL CD	methylphenidate HCl	Y	
ORAL	CPBP 30-70	METHYLPHENIDATE HCL ER	methylphenidate HCl	Y	
ORAL	TABLET	DEXMETHYLPHENIDATE HCL	dexmethylphenidate HCl	Y	
ORAL	TABLET	FOCALIN	dexmethylphenidate HCl	Y	
ORAL	CPBP 50-50	DEXMETHYLPHENIDATE HCL ER	dexmethylphenidate HCl	Y	
ORAL	CPBP 50-50	FOCALIN XR	dexmethylphenidate HCl	Y	
TRANSDERM	PATCH TD24	DAYTRANA	methylphenidate	Y	
ORAL	CAPSULE	ATOMOXETINE HCL	atomoxetine HCl	Y	Y
ORAL	CAPSULE	STRATTERA	atomoxetine HCl	Y	Y
ORAL	TABLET	ADDERALL	dextroamphetamine/amphetamine	Y	
ORAL	TABLET	DEXTROAMPHETAMINE-AMPHETAMINE	dextroamphetamine/amphetamine	Y	
ORAL	CAP ER 24H	ADDERALL XR	dextroamphetamine/amphetamine	Y	
ORAL	CAP ER 24H	DEXTROAMPHETAMINE-AMPHET ER	dextroamphetamine/amphetamine	Y	
ORAL	CAPSULE	VYVANSE	lisdexamfetamine dimesylate	Y	
ORAL	TAB ER 12H	CLONIDINE HCL ER	clonidine HCl	V	Y
ORAL	TAB ER 12H	KAPVAY	clonidine HCl	V	Y
ORAL	TAB ER 24H	GUANFACINE HCL ER	guanfacine HCl	V	Y
ORAL	TAB ER 24H	INTUNIV	guanfacine HCl	V	Y
ORAL	TABLET ER	METADATE ER	methylphenidate HCl	N	
ORAL	TABLET ER	METHYLPHENIDATE ER	methylphenidate HCl	N	
ORAL	TAB ER 24	CONCERTA	methylphenidate HCl	N	
ORAL	TAB ER 24	METHYLPHENIDATE ER	methylphenidate HCl	N	
ORAL	CPBP 50-50	METHYLPHENIDATE ER	methylphenidate HCl	N	
ORAL	CPBP 50-50	METHYLPHENIDATE LA	methylphenidate HCl	N	
ORAL	CPBP 50-50	RITALIN LA	methylphenidate HCl	N	
ORAL	TAB CHEW	METHYLIN	methylphenidate HCl	N	
ORAL	TAB CHEW	METHYLPHENIDATE HCL	methylphenidate HCl	N	
ORAL	SOLUTION	METHYLIN	methylphenidate HCl	N	
ORAL	SOLUTION	METHYLPHENIDATE HCL	methylphenidate HCl	N	
ORAL	CSBP 40-60	APTENSIO XR	methylphenidate HCl	N	
ORAL	SU ER RC24	QUILLIVANT XR	methylphenidate HCl	N	
ORAL	TAB CBP24H	QUILLICHEW ER	methylphenidate HCl	N	
ORAL	TAB RAP BP	COTEMPLA XR-ODT	methylphenidate	N	
ORAL	TABLET	EVEKEO	amphetamine sulfate	N	

ORAL	CAPSULE ER	DEXEDRINE	dextroamphetamine sulfate	N
ORAL	CAPSULE ER	DEXTROAMPHETAMINE SULFATE ER	dextroamphetamine sulfate	N
ORAL	TABLET	DEXEDRINE	dextroamphetamine sulfate	N
ORAL	TABLET	DEXTROAMPHETAMINE SULFATE	dextroamphetamine sulfate	N
ORAL	TABLET	ZENZEDI	dextroamphetamine sulfate	N
ORAL	SOLUTION	DEXTROAMPHETAMINE SULFATE	dextroamphetamine sulfate	N
ORAL	SOLUTION	PROCENTRA	dextroamphetamine sulfate	N
ORAL	TABLET	DESOXYN	methamphetamine HCl	N
ORAL	TABLET	METHAMPHETAMINE HCL	methamphetamine HCl	N
ORAL	CPTP 24HR	MYDAYIS	dextroamphetamine/amphetamine	N
ORAL	TAB CHEW	VYVANSE	lisdexamfetamine dimesylate	N
ORAL	SUS BP 24H	DYANAVEL XR	amphetamine	N
ORAL	TAB RAP BP	ADZENYS XR-ODT	amphetamine	N
ORAL	SUS BP 24H	ADZENYS ER	amphetamine	N

Appendix 2: New Comparative Clinical Trials

A total of 89 citations were manually reviewed from the initial literature search. After further review, 88 citations were excluded because of wrong study design (e.g., observational studies except for in the case of clinically important safety outcomes), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 1 trial is summarized in the table below. The full abstract is included in **Appendix 3**.

Table 1. Description of Comparative Clinical Trials or Observational Trials for Clinically Important Safety Outcomes.

Study	Comparison	Population	Primary Outcome	Results
Quinn PD, et al[8] Retrospective claims study N=2,993,887 Claims from 2005-2014	1. Stimulant* or atomoxetine 2. No medication	Patients 13 years of age and older with ADHD	Risk of substance-related events (i.e., emergency department visits related to substance use disorders) during months in which patients received prescribed stimulant medication or atomoxetine relative to risk during months in which they did not	*Males* 1. 3.1% 2. 4.0% OR 0.76; 95% CI 0.75 to 0.78 *Females* 1. 2.6% 2. 2.8% OR 0.94; 95% CI 0.91 to 0.97

Abbreviations: CI = confidence interval; OR = odds ratio

*Stimulant = amphetamine salt combination, dexmethylphenidate hydrochloride, dextroamphetamine sulfate, lisdexamfetamine dimesylate, methamphetamine hydrochloride, methylphenidate, or methylphenidate hydrochloride

Appendix 3: Abstracts of Comparative Clinical Trials

1. Quinn PD, Chang Z, Hur K, et al. ADHD Medication and Substance-Related Problems. Am J Psychiatry. 2017;174(9):877-885.

   OBJECTIVE: Substance use disorders are major contributors to excess mortality among individuals with attention deficit hyperactivity disorder (ADHD), yet associations between pharmacological ADHD treatment and substance-related problems remain unclear. This study investigated concurrent and long-term associations between ADHD medication treatment and substance-related events. METHOD: The authors analyzed 2005–2014 commercial health care claims from 2,993,887 (47.2% female) adolescent and adult ADHD patients. Within-individual analyses compared the risk of substance-related events (i.e., emergency department visits related to substance use disorders) during months in which patients received prescribed stimulant medication or atomoxetine relative to the risk during months in which they did not. RESULTS: In adjusted within-individual comparisons, relative to periods in which patients did not receive ADHD medication, male patients had 35% lower odds of concurrent substance-related events when receiving medication (odds ratio=0.65, 95% CI=0.64–0.67), and female patients had 31% lower odds of concurrent substance-related events (odds ratio=0.69, 95% CI=0.67–0.71). Moreover, male patients had 19% lower odds of substance-related events 2 years after medication periods (odds ratio=0.81, 95% CI=0.78–0.85), and female patientshad14%lowerodds of substance-related events2years after medication periods (odds ratio=0.86, 95% CI= 0.82–0.91). Sensitivity analyses supported most findings but were less consistent for long-term associations among women. CONCLUSIONS: These results provide evidence that receiving ADHD medication is unlikely to be associated with greater risk of substance-related problems in adolescence or adulthood. Rather, medication was associated with lower concurrent risk of substance-related events and, at least among men, lower long-term risk of future substance-related events.

Appendix 4: Medline Search Strategy on 06/08/2018

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

1 exp Atomoxetine Hydrochloride/	*1069*
2 exp Dexmethylphenidate Hydrochloride/	*54*
3 exp DEXTROAMPHETAMINE/	*6918*
4 exp AMPHETAMINES/	*36198*
5 exp Lisdexamfetamine Dimesylate/	*221*
6 exp METHYLPHENIDATE/	*6698*
7 exp CLONIDINE/	*13009*
8 exp GUANFACINE/	*649*
9 Methamphetamine/	*8493*
10 exp Attention Deficit Disorder with Hyperactivity/	*25633*
11 adhd.mp	*21653*
12 exp "Attention Deficit and Disruptive Behavior Disorders"/	*29288*
13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	*35206*
14 10 or 11 or 12	*34988*
15 13 and 14	*4585*
16 limit 15 to (English language and humans)	*3931*
17 limit 16 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or pragmatic clinical trial or randomized controlled trial or systematic reviews)	*1745*
18 limit 17 to yr="2017-Current"	*78*

Appendix 5: Key Inclusion Criteria

Population	Adult and pediatric patients with attention deficit hyperactivity disorder (ADHD) or attention deficit disorder (ADD)
Intervention	Drugs in ADHD class (**Appendix 1**)
Comparator	Drugs in ADHD class (**Appendix 1**) or placebo if clinically important safety outcomes
Outcomes	Efficacy: symptom improvement, functional capacity, quality of life, time to onset of effectiveness, duration of effectiveness Safety: withdrawals due to adverse events, serious and long term (>12 months) adverse events, misuse/diversion
Timing	Literature from 06/30/17 (end of literature search from last review in 7/2018) – 06/08/18
Setting	Outpatient

Attention Deficit Hyperactivity Disorder (ADHD) Safety Edit

Goals:

- Cover ADHD medications only for diagnoses funded by the OHP and medications consistent with current best practices.
- Promote care by a psychiatrist for patients requiring therapy outside of best-practice guidelines.
- Promote preferred drugs in class.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred drugs on the enforceable preferred drug list.
- Regimens prescribed outside of standard doses and age range (Tables 1 and 2)
- Non-standard polypharmacy (Table 3)

Covered Alternatives:

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

Table 1. FDA-approved and OHP-funded Indications.

	STIMULANTS		NON-STIMULANTS		
Indication	**Methylphenidate and derivatives****	**Amphetamine and derivatives**	**Atomoxetine**	**Clonidine ER**	**Guanfacine ER**
ADHD	Age ≥6 years	Age ≥3 years	Age ≥6 years	Children age 6-17 years only	Children age 6-17 years only
Narcolepsy	Age ≥6 years	Age ≥6 years	Not approved	Not approved	Not approved

See **Table 2 for off-label methylphenidate IR dosing for age ≥ 4 years

Table 2. Standard Age and Maximum Daily Doses.

Drug Type	Generic Name	Minimum Age	Maximum Age	Maximum Daily Dose (adults or children <18 years of age unless otherwise noted)
CNS Stimulant	amphetamine/dextroamphetamine salts IR	3		40 mg
CNS Stimulant	amphetamine/dextroamphetamine salts ER	6		60 mg
CNS Stimulant	dexmethylphenidate IR	6		20 mg
CNS Stimulant	dexmethylphenidate LA	6		40 mg for adults or 30 mg if age <18 years

CNS Stimulant	dextroamphetamine IR	6		40 mg
CNS Stimulant	dextroamphetamine LA	6		60 mg
CNS Stimulant	lisdexamfetamine	6		70 mg
CNS Stimulant	methamphetamine	6	17	not established
CNS Stimulant	methylphenidate IR	4		60 mg
CNS Stimulant	methylphenidate LA	6		72 mg
CNS Stimulant	methylphenidate transdermal	6	17	30 mg
Non-Stimulant	atomoxetine	6		100 mg
Non-Stimulant	clonidine LA	6	17	0.4 mg
Non-Stimulant	guanfacine LA	6	17	4 mg for adjunctive therapy in ages 6-17 years and for monotherapy in ages 6-12 years 7 mg for monotherapy in ages 13-17 years

Abbreviations: IR = immediate-release formulation; LA = long-acting formulation (extended-release, sustained-release, etc.)

Table 3. Standard Combination Therapy for ADHD

Age Group	Standard Combination Therapy
Age <6 years*	Combination therapy not recommended
Age 6-17 years*	1 CNS Stimulant Formulation (LA or IR) + Guanfacine LA 1 CNS Stimulant Formulation (LA or IR) + Clonidine LA
Age ≥18 years**	Combination therapy not recommended

Abbreviations: IR = immediate-release formulation; LA = long-acting formulation (extended-release, sustained-release, etc.)
* As recommended by the American Academy of Pediatrics 2011 Guidelines www.pediatrics.org/cgi/doi/10.1542/peds.2011-2654
**As identified by Drug Class Review: Pharmacologic Treatments for Attention Deficit Hyperactivity Disorder: Drug Effectiveness Review Project, 2011.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the drug being used to treat an OHP-funded condition?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by OHP.
3. Is the requested drug on the PDL?	**Yes:** Go to #5	**No:** Go to #4

Approval Criteria		
4. Will the prescriber consider a change to a preferred agent? Message: • Preferred drugs are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of preferred alternatives	**No:** Go to #5
5. Is the request for an approved FDA diagnosis ~~indication~~ defined in Table 1?	**Yes:** Go to #6	**No:** Go to #9
6. Are the patient's age and the prescribed dose within the limits defined in Table 2?	**Yes:** Go to #7	**No:** Go to #9
7. Is the prescribed drug the only stimulant or non-stimulant filled in the last 30 days?	**Yes:** Approve for up to 12 months	**No:** Go to #8
8. Is the multi-drug regimen considered a standard combination as defined in Table 3?	**Yes:** Approve for up to 12 months	**No:** Go to #9
9. Was the drug regimen developed by, or in consultation with, a psychiatrist, developmental pediatrician, psychiatric nurse practitioner, sleep specialist or neurologist?	**Yes:** Document name and contact information of consulting provider and approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness. Doses exceeding defined limits or non-recommended multi-drug regimens of stimulants and/or non-stimulants are only approved when prescribed by a psychiatrist or in consultation with a mental health specialist. May approve continuation of existing therapy once up to 90 days to allow time to consult with a mental health specialist.

P&T Review: *9/18 (JP); 5/16; 3/16 (AG); 5/14; 9/09; 12/08; 2/06; 11/05; 9/05; 5/05; 2/01; 9/00; 5/00*
Implementation: *TBD; 10/13/16; 7/1/16; 10/9/14; 1/1/15; 9/27/14; 1/1/10; 7/1/06; 2/23/06; 11/15/05*

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Drug Class Review: Vaginal Antibiotics

Date of Review: September 2018 **End Date of Literature Search:** 06/25/2018

Purpose for Class Review:
This is the first drug class review for vaginal antibiotics, prompted by the approval of secnidazole, a new oral therapy approved in 2017 for bacterial vaginosis (BV).

Research Questions:
1. In patients with BV or trichomoniasis, what is the comparative evidence for the effectiveness of vaginal antibiotics based on efficacy outcomes (e.g., clinical resolution, recurrence, symptom resolution)?
2. In patients with BV or trichomoniasis, what is the comparative evidence for the harms of vaginal antibiotics?
3. Are there subpopulations of patients requiring vaginal antibiotics for which specific therapies may be more effective or associated with less harm?

Conclusions:
- This drug class review is limited by lack of high quality evidence. A majority of the evidence comes from studies with small sample sizes, unclear risk of bias (in part due to older studies with methodological challenges), industry funding, and limited number of trials; therefore, strong conclusions of comparative efficacy cannot be made. There is insufficient comparative evidence in women with BV or trichomoniasis that newer treatments or treatments with shorter days of therapy are superior to older therapies or therapies requiring longer treatment durations. Oral metronidazole and tinidazole have Boxed Warnings for possible association with carcinogenicity in mice and rats and oral clindamycin has a Boxed Warning for *clostridium difficile* associated diarrhea.
- Metronidazole and clindamycin have the most evidence for the treatment of BV in non-pregnant women and are recommended first line by Centers for Disease Control (CDC) guidelines (low to moderate quality of evidence).[1,2] There is insufficient evidence that one oral or topical treatment for BV is superior to another.
- There is no data to support the treatment of sexual partners of women with symptomatic BV. Studies showed no benefit of clinical or symptomatic improvement (high strength of evidence).[3]
- There is low strength of evidence from one, small, phase 3 trial that a single dose of oral secnidazole is more effective than placebo in eradication of BV with an ARR of 34% and NNT of 3 at day 21-30 of follow-up.[4]
- In pregnant women with BV, there is low quality evidence that antimicrobial treatment is effective for bacterial eradication, but there is insufficient evidence to show that treatment impacts pregnancy outcomes (preterm birth, late miscarriage).[5]
- In women with trichomoniasis, treatment with nitroimidazole antimicrobials results in higher cure rates compared to no treatment (low strength of evidence). There is insufficient evidence of one nitroimidazole superiority over another.[6]

- The UK treatment guidelines recommend metronidazole, 1-7 days of treatment, as first line therapy for women with trichomoniasis based on high quality evidence.[7]

Recommendations:

- Recommend non-preferred drugs in the class be subject to the Preferred Drug List – Non-Preferred Drugs in Select PDL Class prior authorization (PA) criteria (**Appendix 3**).
- Recommend brand name metronidazole, Nuvessa, remain non-preferred as currently assigned. Recommend secnidazole be designated as non-preferred.
- Recommend at least one metronidazole and clindamycin formulation be preferred.
- Evaluate comparative drug costs in executive session.

Background:

Bacterial vaginosis is an infection that is common in women of reproductive-age (ages 14-49 years) which occurs in approximately 29% of the general population.[8] BV is most often caused by the following bacteria: *Gardnerella vaginalis*, *Prevotella* species, *Porphyromonas* species, *Bacteroides* species, *Peptostreptococcus* species, *Mycoplasma hominis* and *Ureaplasma urealyticum*. Amsel's criteria is often used for diagnosis, which requires 3 of the 4 following criteria: vaginal pH >4.5, release of fishy smell on the addition of alkali (10% potassium hydroxide), characteristic discharge on examination, and presence of 'clue cells' on microscopy of vaginal fluid mixed with normal saline.[1,9] A Gram-stained vaginal smear is also used for diagnosis. The Nugent scoring system (NSS) is a validated method to determine the presence of BV by interpretation of a Gram stain of vaginal secretions.[10] Scores of 0-3 are considered normal, with a positive test indicated by a score of 7 to 10.[8]

Infections can be asymptomatic or symptomatic, with treatment recommended for symptomatic women with the goal of symptom elimination. In pregnant women, preterm delivery is higher in women with BV; however, treatment of asymptomatic infections has not shown to decrease the risk of preterm birth.[8] Therefore, universal screening for BV in pregnant women is not recommended; however women diagnosed with BV during pregnancy should be treated. Women who are asymptomatic and are undergoing an abortion or hysterectomy should also be treated to prevent postoperative infections.[8] The presence of BV is thought to increase the risk of other sexually transmitted diseases (i.e., human immunodeficiency virus, herpes simplex virus type 2, gonorrhoeae, chlamydia and trichomoniasis).[10] Treatment of sexual partners of women with BV is not recommended.

Common therapies to treat BV are metronidazole or clindamycin orally or intravaginally, with cure rates of up to 70% to 80%.[1] Seven days of oral treatment is recommended for metronidazole versus five days of vaginal therapy. A single-dose intravaginal metronidazole dose is available, but the effectiveness compared to multiple day regimens is unknown. Clindamycin is available as a seven-day course of intravaginal cream, seven days of oral therapy, clindamycin ovules for three days and a one-day bioadhesive treatment. The treatment of choice is the seven-day intravaginal regimen as the other delivery options are thought to be associated with a lower incidence of eradication of BV.[1] Oral metronidazole or oral clindamycin are recommended for symptomatic patients who are pregnant. Choice of regimen is dependent upon medication adverse events, cost, patient preference and route of administration. Oral delivery methods are more convenient but are associated with a higher incidence of systemic adverse events including headache, nausea and vomiting. Important outcomes for BV treatments include eradication of symptoms and cure rates.

Alternative treatment options include tinidazole and secnidazole. They should be given as 1 gm for 5 days.[11] Shorter courses of higher doses are used, but are associated with more side effects and reduced efficacy. Secnidazole has been recently approved as a single-dose option with similar eradication rates as metronidazole.[12] There is insufficient evidence to recommend the use of probiotics for adjunctive treatment or the primary treatment of BV.[8]

In addition to BV, vaginal antibiotics are used for trichomoniasis, which is a flagellated protozoan (*T.vaginalis)* which may infect the urogenital tract. Detection of *T.vaginalis* is done microscopically. Newer monoclonal antibody-based point of care testing and nucleic acid amplification test (NAAT) detect trichomoniasis with a high degree of sensitivity but are not used routinely in clinical settings.[2,13] Trichomoniasis is the most common non-viral sexually transmitted disease, affecting approximately 3.7 million persons.[8] Coinfections with BV is common in women with rates as high as 80%. Prevalence of trichomoniasis in the United States is thought to range from 1.3% (non-Hispanic white women) and to up to 13.3% (non-Hispanic black women). Discharge, burning and pain are common symptoms with trichomoniasis; however, asymptomatic carrier infections are also common. Diagnosis is made by a laboratory test confirming the presence of trichomoniasis. Treatment of trichomoniasis is recommended to prevent the development of urethritis or cystitis. Increased risk of acquiring HIV may occur if trichomoniasis remains untreated, in addition to an increase in the incidence of cervical intraepithelial neoplasia and cervical carcinoma.[13] The rate of preterm birth and other undesirable obstetric outcomes have been seen in pregnant women with trichomoniasis.

Patients experience a spontaneous cure in up to 25% of trichomoniasis cases and only approximately 5% of cases develop resistance.[13] Treatment of asymptomatic and symptomatic women and men is recommended to prevent transmission to sexual partners. Partners should also be evaluated and treated. Treatment regimens recommended for trichomoniasis are a single 2 gm dose of either oral metronidazole or tinidazole. Cure rates are as high as 88% with metronidazole after a single dose versus 92% for a 5-7 day course.[13] The recommended regimen for pregnant women is 2 grams orally of metronidazole or 500 mg twice daily for 5-7 days. Patients with HIV should be treated twice daily for seven days.

The vaginal antibiotic class has a low volume of claims and represents only a small percentage of overall cost burden to the Oregon Health Plan (OHP) system. The only drug with a non-preferred designation is the branded metronidazole vaginal gel, Nuvessa, which had no utilization last quarter. Eighty-five percent of the utilization is for generic metronidazole gel.

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

Table 1. Indications and Dosing.

Drug Name (Manufacturer)	Indication(s)	Strength/Route	Dose and Frequency
Lincosamides			
Clinidamycin[14]	BV	300 mg orally	1 capsule twice daily for 7 days
Clindaymcin[15]	BV	100 mg vaginally	1 suppository for 3 or 7 days
Clindamycin (Clindesse)[16]	BV	100 mg vaginally	1 suppository as one dose
5-Nitro-imidazoles			
Metronidazole[17]	BV or trichomoniasis	500 mg orally	1 tablet twice daily for 7 days
Metronidazole[18]	BV or trichomoniasis	37.5 mg vaginally	1 applicator once daily for 5 days
Metronidazole (Nuvessa)[19]	BV or trichomoniasis	65 mg vaginally	1 applicator at bedtime
Tinidazole[11]	Trichomoniasis	2 grams	As one dose
Tinidazole[11]	BV	1- 2 grams orally	2 grams as one dose or 1 gram for 5 days
Secnidazole[12]	BV	2 grams orally	1 packet of granules as a single dose

Abbreviations: BV = bacterial vaginosis

Table 2. Summary of Pivotal Studies Completed.

Study	Comparison	Population	Primary Outcome	Results
Schwebeke, et al[4] Phase 3, RCT, PC	Secnidazole 2 gm granules X 1 dose (S) vs. Placebo granules X 1 dose (P)	Non-pregnant women mean age of 31 years with BV(n=189)	Proportion of clinical outcome responders at follow-up visit days 21-30*	S: 57 (53%) P: 11 (19.3%) ARR 34%/NNT 3; p<0.001
Hillier, et al[20] Phase 2, RCT, DB, PC^	Secnidazole 1 gm granules X 1 dose (S1) vs. Secnidazole 2 gm granules X 1 dose (S2) vs. Placebo granules (P)	Adult women with a median age of 33 years and BV	Clinical cure 21-30 days after treatment*	S1: 33 (51.6%) S2: 42 (67.7%) P: 11 (17.7%) S1 vs. P: ARR 34%/NNT 3; p<0.001 S2 vs. P: ARR 50%/NNT 2; p<0.001
Key: * Clinical outcome responders defined as: normal vaginal discharge, negative 10% potassium hydroxide whiff test and Clue cells <20% of total epithelial cell count on microscopic examination of the vaginal wet mount, using saline as the test of cure/end of study visit ^ Used for FDA approval				
Abbreviations: ARR – absolute risk reduction; BV – bacterial vaginosis, DB – double-blind; NNT – number needed to treat; PC – placebo controlled; RCT – randomized controlled trial				

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Institute for Clinical and Economic Review (ICER), 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. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

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:

Bacterial Vaginosis

Cochrane – Antibiotic Treatment for the Sexual Partners of Women with Bacterial Vaginosis

A 2016 Cochrane review identified seven randomized controlled trials with 1026 participants.[3] Five trials were placebo controlled and two trials had no comparator. Nitroimidazoles were used for treatment in six trials, four trials used metronidazole and two trials used tinidazole. Patients were sexual partners of

adult women between the ages of 17-56 years with symptomatic BV.[3] Four trials were industry funded. Most studies had a low risk of bias for random sequence generation, blinding and outcome assessment. Seventy-five percent of studies had an unclear risk of allocation concealment. Primary outcomes were BV recurrence, clinical improvement (based on Amsel's criteria or other clinical criteria), symptomatic improvement and serious adverse events.

High quality evidence found clinical improvement in women at week 1-4 of follow-up to be similar with antibiotic treatment compared to placebo (RR 1.02; 95% CI, 0.94 to 1.11). Results were also similar at week 4-12 of follow-up (RR 0.98; 95% CI, 0.90 to 1.07).[3] Symptomatic improvement during the first week was similar with treatment and placebo (RR 1.06; 95% CI, 1.00 to 1.12; 3 studies) based on high quality evidence. Recurrence of BV after 4 weeks was not different between antimicrobial treatment and placebo in women, as demonstrated by a RR of 1.0 (95% CI, 0.67 to 1.52; 3 studies); however, evidence was considered to low quality.[3] Sexual partners report an increased incidence of adverse reactions. Limitations to the evidence included limited number of trials for each comparison and risk of publication bias due to industry funding of studies.

Cochrane – The Effects of Antimicrobial Therapy on Bacterial Vaginosis in Non-Pregnant Women
A Cochrane review in 2010 reviewed the evidence for the use of antimicrobials for the treatment of BV in adult women who were not pregnant.[1] Twenty-four trials were identified that evaluated the following antibiotics: clindamycin (topical and oral), metronidazole (oral and topical), secnidazole, triple sulfonamide cream, hydrogen peroxide douche, and oral lactobacillus. Tinidazole was included in the search criteria but no studies were included. Nine of the 24 were funded by industry. Patients ranged from 15-75 years and all had a diagnosis of symptomatic BV.[1] The primary outcome was treatment failure determined by the Amsel criteria at 7-30 days after treatment. The evidence was assessed for risk of bias but was not given an overall evidence grade by Cochrane.

Results for the outcome of clinical failure that resulted in either a) analysis of 2 or more studies b) were statistically significant are presented in **Table 3**.[1] Comparisons of individual studies that resulted in insufficient evidence to draw conclusions on clinical cure rates resulted from the following comparisons: clindamycin ovule versus clindamycin cream, clindamycin ovule versus lactobacilli, clindamycin cream versus oral tinidazole, 2% clindamycin cream versus triple sulfonamide cream, polyhexamethylene biguanide douche versus clindamycin cream, cefadroxil versus metronidazole, secnidazole 1 gm versus secnidazole 2 gm, and lactobacillus versus metronidazole.[1] Limitations to the evidence includes small study sample sizes, multiple studies with unclear risk of bias in randomization and allocation, large confidence intervals and high heterogeneity in some of the meta-analyses.

Table 3. Clinical Failure Results for Antimicrobial Therapy for Bacterial Vaginosis.[1]

Comparison	Number of studies/patients	Limitations	Results for clinical failure	Adverse events
Topical metronidazole vs. Placebo (P)	2/191	• Small study size • Unclear allocation bias in both studies	TM: 44 (36%) P: 45 (66%) RR 0.59 (95% CI, 0.44 to 0.79) *Favors of metronidazole*	Candida infection: TM: 6 (16%) P: 0 (0%) ARR 16/NNH 7
Topical clindamycin (TC) vs. Placebo (P)	2/285	• Small study size • Unclear randomization in both studies • Unclear allocation concealment in one study	TC: 18 (12%) P: 64 (50%) RR 0.19 (95% CI, 0.09 to 0.41) *Favors of clindamycin*	Not reported

Metronidazole (M) vs. Clindamycin (C)	6/1189	• Unclear allocation concealment (4 studies) • Unclear randomization allocation (2 studies) • One open-label study	M: 48 (8%) C: 51 (9%) RR 1.06 (95% CI, 0.64 to 1.75) *No significant difference between treatments**	Metallic taste: 0.09 (95% CI, 0.01 to 0.68) Nausea/vomiting: 0.27 (95% CI, 0.11 to 0.69)
Tinidazole vs. Metronidazole	2/175	• Both studies open-label with unclear randomization allocation • High heterogeneity (I^2= 42%)	*No significant difference between treatments*	Rates of nausea and vomiting were similar
Oral metronidazole (OM) vs. Clindamycin cream (CC)	3/528	• Unclear allocation concealment in 2 studies • High heterogeneity (I^2= 40%)	OM: 17 (6%) CC: 26 (10%) RR 1.43 (95% CI, 0.57 to 3.60) *No significant difference between treatments*	Metallic taste: RR 0.08 (95% CI, 0.1 to 0.59) Nausea and vomiting: RR 0.23 (95% CI, 0.10 to 0.51)
Single hydrogen peroxide douche (HP) vs. Single dose metronidazole (M)	1/142	• Low risk of bias for all domains	HP: 27 (38%) M: 15 (21%) ARR 17/NNT 6 RR 1.75 (95% CI, 1.02 to 3.00) *Favors metronidazole*	Reduced eating and vomiting: HP: 10 (14%) M: 34 (62%) vaginal irritation: HP: 24 (33%) M: 10 (14%)
Metronidazole vs. Metronidazole + azithromycin	3/554	• Low risk of bias for all domains	M: 36 (27%) M+A: 75 (18%) RR 0.65 (95% CI, 0.46 to 0.92) *Favors metronidazole + azithromycin*	Incidence of candida and nausea were similar in both groups

Cochrane – Antibiotics for Treating Bacterial Vaginosis in Pregnancy

A 2013 review assessed the efficacy of antimicrobial therapies in women who were pregnant with a diagnosis of asymptomatic or symptomatic BV.[8] Twenty-one trials (n=7847 women) of good quality with an overall low risk of bias were included in the review. Inclusion criteria required a Nugent score of at least 4, suggesting inclusion of borderline BV infection and patients with a BV diagnosis. Evidence was identified for the following treatments: metronidazole and clindamycin. Data was analyzed for risk of bias, but overall evidence grades were not provided. Bacterial eradication, risk of late miscarriage, and incidence of pre-term birth were the main outcomes of interest.

Results for the primary outcomes are presented in **Table 4**.[8] All other outcomes were based on very low quality evidence, primarily limited studies of small sample size. There was no difference identified in the following subgroup analyses: preterm birth before 34 weeks, 32 weeks or low birthweight. Similar limitations as described in the above Cochrane review are applicable to this review as well. Unfortunately, high quality evidence for BV treatment is lacking.[8]

Table 4. Outcomes in Pregnant Women Treated for Bacterial Vaginosis.[8]

Outcome	Number of studies/patients	Comparison	Results	Limitations	Adverse events
Preterm Birth*	13/6491	Any antimicrobial vs. Placebo	RR 0.88 (95% CI, 0.71 to 1.09) *No significant difference between treatments*	Moderate heterogeneity (I^2= 48%)	Higher incidence of adverse events compared to placebo
	1/258	Oral metronidazole + erythromycin vs. Placebo	RR 0.64 (95% CI, 47 to 0.88) *Favors metronidazole + erythromycin*	One small study	Same as above
Late Miscarriage	2/1270	Any antimicrobial vs. Placebo	RR 0.20 (95% CI, 0.05 to 0.76) *Favors antimicrobial treatment*	NR	Same as above
Failure of Test of Cure (eradication failure)	10/4403	Any antimicrobial vs. Placebo	RR 0.42 (95% CI, 0.31 to 0.56) *Favors antimicrobial treatment*	High heterogeneity (I^2=91%)	Same as above
Key: * Defined as before 37 weeks					
Abbreviations: CI – confidence interval; NR – not reported; RR – risk ratio					

Trichomoniasis

Cochrane – Interventions for Treating Trichomoniasis in Women

A 2009 review assessed the treatment of symptomatic and asymptomatic trichomoniasis (confirmed by laboratory testing) in women who were not pregnant.[13] Fifty-four trials were identified, 30 had moderate risk of allocation concealment bias, 16 had low risk and 8 had high risk. Outcome assessment was blinded in 13/54 trials and was unclear in the remaining trials. Evidence was identified for treatments of miconazole, ornidazole (not available in the US) and tinidazole. All studies were small, enrolling less than 200 patients in most studies. Studies were assessed for risk of bias, but the evidence was not given an evidence grade.[13]

Evidence supports the higher cure rates with antimicrobials compared to placebo (**Table 5**).[13] Use of any nitroimidazole resulted in parasitological cure, regardless of treatment course duration. Limitations to the systematic review and meta-analysis include small sample size, limited number of studies, high attrition rates and lack of comparative efficacy studies between treatments.

Table 5. Cure Rates of Trichomoniasis Treatment with Nitroimidazoles^ in Women.[13]

Outcome	Number of studies/patients	Comparison	Results	Limitations	Adverse events
No Parasitological Cure (day 4 to 4 weeks)	6/672	Treatment vs. No treatment	RR 0.19 (95% CI, 0.15 to 0.23) *Favors treatment*	High heterogeneity (I^2=96%)	Metallic taste, nausea and vomiting were more common with treatment

No Parasitological Cure (f/u day not stated)	4/427	Short treatment (1-2 doses) vs. Long treatment (5-10 days)	RR 1.12 (95% CI, 0.58 to 2.16) *No significant difference between treatments*	Moderate heterogeneity (I^2=29%)	Short term treatment associated with a higher rate of adverse events
No Parasitological Cure (2 weeks)	4/426	Oral + intravaginal treatment vs. Oral treatment	RR 3.00 (95% CI, 1.10 to 8.16) *Favors combination treatment*	Individual trials were small	Not studied
Key: ^ metronidazole, tinidazole and ornidazole Abbreviations: CI – confidence interval; RR – risk ratio					

Cochrane – Interventions for Trichomoniasis in Pregnancy
A 2011 Cochrane review found insufficient evidence to determine the effect of treating trichomoniasis on pregnancy outcomes.[21]

Guidelines:
Centers for Disease Control – Sexually Transmitted Diseases Treatment Guidelines
In 2015, the CDC released new guidance on treatment recommendations for sexually transmitted disease.[8] Guidelines were authored by workgroup members from federal, state, and local health departments; clinical providers; and professional organizations. The chair had no conflicts of interest; however, sixteen of the workgroup members have conflicts with industry. A systematic review of the literature was performed and the literature was graded using the United Services Preventative Services Task Forces (USPSTF) modified rating system. Recommendations were reviewed by a second independent panel of public health and clinical experts. Evidence tables and assessment of the individual studies were provided; however, individual grades of the evidence were not provided for evidence pertaining to BV.

Table 6. United Services Preventative Services Task Forces (USPSTF) Modified Rating System.[8]

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the clinical considerations section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

CDC guidelines recommend treatment of symptomatic women with BV to relieve symptoms and reduce the risk of acquiring *C. trachomatis*, *N. gonorrhoeae*, *T. vaginalis*, HIV and herpes simplex type 2.[8] Recommended treatment options are presented in **Table 7,** and alternative treatments are presented in **Table 8**. Recurrence may be treated with the same regimen or an alternative therapy. For multiple recurrences, guidelines recommend 0.75% metronidazole gel twice weekly for 4-6 months. Other suppressive options include seven days of metronidazole or tinidazole followed by intravaginal boric acid 600 mg daily for 21 days followed by 0.75% metronidazole gel twice weekly for 4-6 months. Monthly 2 gm metronidazole orally with fluconazole 150 mg may also be an option.

Table 7. Bacterial Vaginosis Recommended Treatment Regimens.[8]

Therapy	Dosing Regimen
Metronidazole	500 mg twice daily orally for 7 days
Metronidazole Gel	0.75% applicator intravaginally once daily for 5 days
Clindamycin Cream	2% applicator intravaginally at bedtime for 7 days
Pregnant Women	
Metronidazole	250 mg orally three times daily for 7 days or 500 mg orally twice daily for 7 days

Table 8. Bacterial Vaginosis Alternative Treatment Regimens.[8]

Therapy	Dosing Regimen
Tinidazole	2 gm orally once daily for 2 days
Tinidazole	1 gm orally once daily for 5 days
Clindamycin Ovules	100 mg intravaginally at bedtime for 3 days

Trichomoniasis treatment is used to reduce symptoms as well as transmission. The recommended treatments were based on an evidence grade of A-B (**Table 9**). Similar efficacy and safety of treatment options for trichomoniasis have been demonstrated. A reduced incidence of gastrointestinal side effects has been demonstrated with tinidazole.

Table 9. Treatment Options for Trichomoniasis.[8]

Recommended Therapy		
Metronidazole	2 gm orally in a single dose	84% to 98% cure rates
Tinidazole	2 gm orally in a single dose	92% to 100% cure rates
Alternative Therapy Options		
Metronidazole	500 mg orally twice daily for 7 days	84% to 98% cure rates

United Kingdom National Guideline on the Management of Trichomonas Vaginalis

The British Association for Sexual Health and HIV (BASHH) authored an update to its 2007 guideline on the management of trichomonas in 2014.[13] The guideline is accredited by the National Institute for Health and Care Excellence (NICE) which ensures that the guidelines were created based on the AGREE tool that is used

to distinguish high quality guidelines. The guideline was funded internally and one of 6 authors reported receiving funding from industry. The assignment of strength of evidence is provided in **Table 10,** and the rating scheme is provided in **Table 11**.

Table 10. Levels of Evidence.[13]

Level	Type of Evidence
Ia	Evidence obtained from meta-analysis of randomized controlled trials
Ib	Evidence obtained from at least one randomized controlled trials
IIa	Evidence obtained from at least one well-designed controlled study without randomization
IIb	Evidence obtained from at least one type of well-designed quasi-experimental study
III	Evidence obtained from well-designed, non-experimental descriptive studies, such as comparative studies, correlation studies and case control studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authors

Table 11. Grading of Recommendations. [13]

Grade	Recommendations
A (Evidence levels Ia, Ib)	Requires at least one randomized controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation
B (Evidence levels IIa, IIb, II)	Requires availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommendation
C (Evidence level IV)	Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality

Treatment recommendations are presented in **Table 12**.[13] First-line treatment recommendation is for metronidazole given as a single dose or for up to 7 days. Metronidazole is also recommended in women who are pregnant, but high-dose regimens are advised against. Tinidazole is a contraindicated in the first trimester and the safety of use has not been well researched.[13] Limited evidence suggests that single dose regimens of metronidazole are not as effective as metronidazole given twice daily for 7 days in women with HIV. Guidelines recommend a repeat of a 7-day course of standard therapy for patients who are non-responsive to standard therapy (Evidence Level III).[13] A higher dose regimen of nitroimidazole is recommended for patients failing the subsequent regimens (**Table 7**). Guidance recommends the treatment of sexual partners.

Table 12. UK Guidelines for Treatment of Trichomonas.[13]

Treatment	Dose	Evidence Level / Grade
Metronidazole	2 gm orally as a single dose	Ia / A
Metronidazole	400-500 mg twice daily for 5-7 days	Ia / A
Tinidazole (alternative regimen due to cost)	2 gm orally as a single dose	Ia / A
Non-response to standard trichomonas therapy		
Metronidazole	400-500 mg twice daily for 7 days	III
High-dose nitroimidazole for non-responsive trichomonas for patients failing second regimen		

Metronidazole	2 gm daily for 5-7 days	III
Metronidazole	800 mg three times daily for 7 days	III
Tinidazole	2 gm daily for 5-7 days	III
Higher-dose nitroimidazole for non-responsive trichomonas for patients failing third regimen		
Tinidazole	1 gm twice daily or three times daily for 14 days	III
Tinidazole	2 gm twice daily for 14 days	III
Tinidazole intravaginal	500 mg twice daily for 14 days	III

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Appendix 1: Specific Drug Information for Drugs in the Class

Generic	Brand	Route	FormDesc	PDL
clindamycin	CLINDAMYCIN	PO	CAPSULES	
clindamycin phosphate	CLEOCIN	VG	CREAM/APPL	
clindamycin phosphate	CLINDAMYCIN PHOSPHATE	VG	CREAM/APPL	
clindamycin phosphate	CLINDESSE	VG	CRM ER (G)	
clindamycin phosphate	CLEOCIN	VG	SUPP.VAG	
metronidazole	METRONIDAZOLE	PO	TABLET	
metronidazole	METROGEL-VAGINAL	VG	GEL W/APPL	
metronidazole	METRONIDAZOLE	VG	GEL W/APPL	
metronidazole	NUVESSA	VG	GEL W/APPL	N
metronidazole	VANDAZOLE	VG	GEL W/APPL	
tinidazole	TINDAMAX	PO	TABLET	
secnidazole	SOLOSEC	PO	GRANDR PKT	

Table 13. Clinical Pharmacology and Pharmacokinetics.

Drug Name	Mechanism of Action	Absorption	Metabolism/Excretion	Pharmacokinetics (mean)
Clindamycin capsules[14]	Inhibition of bacterial protein synthesis by binding to the 23S RNA of the 50S subunit of the ribosome.	90% when administered orally	CYP3A4 with minor contribution from CYP3A5 forming clindamycin sulfoxide and N-desmethylclindamycin. 10% urine, 3.6% feces and the majority excreted as bioinactive metabolites.	• Half-life: 2.4 hours • Cmax: 2.50 mcg/mL • AUC: Not reported • Vd: Not reported
Clindamycin phosphate vaginal cream[15]	Inhibition of bacterial protein synthesis by binding to the 23S RNA of the 50S subunit of the ribosome.	5% systemic absorption	NA	• Half-life: 1.5 to 2.6 hours • Cmax: 16-18 ng/mL • AUC: Not reported • Vd: Not reported
Clindamycin phosphate vaginal cream (Clindesse®)[16]	Inhibition of bacterial protein synthesis by binding to the 23S RNA of the 50S subunit of the ribosome.	Minimal systemic absorption	NA	• Half-life: Not reported • Cmax: 6.6 ng/mL • AUC: 175 ng/mL • Vd: Not reported
Metronidazole tablets[17]	Nitroimidazole antibacterial that works in an anaerobic	Well absorbed (specific percentage not stated)	60-80% in the urine 6-15% in the feces	• Half-life: 8 hours • Cmax: 6 mcg/mL – 40 mcg/mL (dose dependent)

	environment against most obligate anaerobes.			• AUC: 175 ng/mL • Vd: Not reported
Metronidazole vaginal gel 0.75% and 1.3%[18]	Nitroimidazole antibacterial that works in an anaerobic environment against most obligate anaerobes. The exact mechanism is unknown.	Minimal systemic exposure	NA	• Half-life: Not reported • Cmax: 214-294 ng/mL • AUC: 5,434-5,989 ng•hr/mL • Vd: Not reported
Tinidazole tablets[11]	Antiprotozoal, antibacterial agent	Completely absorbed	CYP3A4 20-25% in the urine 12% in the feces	• Half-life: 12-14 hours • Cmax: 47.7 ng/mL • AUC: 901.6 ng•hr/mL • Vd: 50 L
Secnidazole (Solosec™) granules[12]	Nitroimidazole antimicrobial thought to interfere with bacterial DNA synthesis of susceptible isolates.	Not reported	CYP450 and 15% is excreted in the urine	• Half-life: 17 hours • Cmax: 45.4 mcg/mL • AUC: 1331.6 mcg•hr/mL • Vd: 42 L
Abbreviations: AUC – area under the curve; Cmax – maximum concentration; NA – not applicable; Vd – volume of distribution				

Table 14. Use in Specific Populations.

Drug Name	Use in Renal Impairment	Use in hepatic impairment	Pregnancy
Clindamycin capsules[14]	Half-life may increase slightly in patients with markedly reduced renal function	Moderate to severe liver disease may prolong the half-life	May be used in the second and third trimesters. Use in first trimester only if clearly needed
Clindamycin phosphate vaginal cream*[15]	Not reported	Not reported	May be used in pregnant patients if clearly needed
Metronidazole tablets[17]	May accumulate metronidazole metabolites in end-stage renal disease. Monitor for adverse events.	In severe hepatic impairment (Child-Pugh C) a dose reduction is recommended. Monitor for adverse events in mild to moderate hepatic impairment	Contraindicated in the first trimester of pregnancy
Metronidazole vaginal gel[18]	Not reported	Use caution in severe hepatic disease	No data in pregnant women
Tinidazole tablets[11]	No dosage adjustment for severe renal failure	Use with caution in hepatic impairment	Contradicted in first trimester, not recommended
Secnidazole (Solosec™) granules[12]	Not reported	Not reported	Insufficient data
*** Includes Clindesse® formulation**			

Drug Safety:

Boxed Warnings:
Clindamycin oral: The use of clindamycin has been associated with *Clostridium difficile* diarrhea which may result in mild diarrhea to fatal colitis.
Metronidazole oral: Metronidazole has been shown to be carcinogenic in mice and rats. Use only for indicated conditions.
Tinidazole: Carcinogenicity has not been demonstrated in tinidazole studies, but due to the structural commonalities with metronidazole, tinidazole also has a Boxed Warning for carcinogenicity in mice and rats. Tinidazole should only be used for approved indications.

Risk Evaluation Mitigation Strategy Programs:
None

Contraindications:
Clindamycin: hypersensitivity reactions to clindamycin or history of regional enteritis, ulcerative colitis, or a history of *C. difficile*-associated diarrhea.
Metronidazole: hypersensitivity reactions to metronidazole, concomitant use with disulfiram, concomitant use with alcohol.
Tinidazole: hypersensitivity reactions to tinidazole, first trimester pregnancy, and nursing moms.
Secnidazole: hypersensitivity reactions to secnidazole.

Table 15. Summary of Warnings and Precautions.

Warning/Precaution	Clindamycin capsules	Clindamycin vaginal cream	Metronidazole tablets	Metronidazole vaginal gel	Tinidazole tablets	Secnidazole granules
C. difficile associated diarrhea	X	X				
Anaphylactic and severe hypersensitivity reactions	X					
Use cautiously in patients with a history of bowel disease	X	X				
Use cautiously in atopic individuals	X					
Breakdown of latex or rubber products (i.e., condoms, diaphragms)		X				
May cause fungal infections			X	X	X	X
May cause mild/transient leukopenia			X		X	
May cause transient neutropenia					X	
Carcinogenic in mice and rats			X	X	X	X
Cannot be used with disulfiram or alcohol			X	X	X	
Risk of central and peripheral nervous system effects			X	X		

Hepatotoxicity and death in patients with Cockayne Syndrome			X			
First trimester pregnancy / nursing					X	
Seizures and neuropathy					X	

Appendix 2: Medline Search Strategy

Database(s): Ovid MEDLINE(R) 1946 to June Week 4 2018
Search Strategy:

#	Searches	Results
1	clindamycin phosphate.mp.	322
2	clindamycin.mp. or CLINDAMYCIN/	10369
3	metronidazole.mp. or METRONIDAZOLE/	16984
4	tinidazole.mp. or TINIDAZOLE/	1311
5	secnidazole.mp.	129
6	1 or 2 or 3 or 4 or 5	26690
7	limit 6 to (english language and humans and yr="2003 -Current")	8456
8	limit 7 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or systematic reviews)	399

Preferred Drug List (PDL) – Non-Preferred Drugs in Select PDL Classes

Goal(s):

- Ensure that non-preferred drugs are used appropriately for OHP-funded conditions.

Initiative:

- PDL: Preferred Drug List

Length of Authorization:

- Up to 6 months

Requires PA:

- Non-preferred drugs

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is this an OHP-funded diagnosis?	**Yes**: Go to #4	**No**: Go to #5

Approval Criteria		
4. Will the prescriber consider a change to a preferred product? Message: Preferred products do not generally require a PA. Preferred products are evidence-based and reviewed for comparative effectiveness and safety by the P&T Committee.	**Yes**: Inform prescriber of covered alternatives in class.	**No**: Approve until anticipated formal review by the P&T committee, for 6 months, or for length of the prescription, whichever is less.
5. RPh only: All other indications need to be evaluated as to whether they are a funded diagnosis on the OHP prioritized list. • If funded and clinic provides supporting literature: Approve until anticipated formal review by the P&T committee, for 6 months, or for length of the prescription, whichever is less. • If not funded: Deny; not funded by the OHP.		

P&T / DUR Review: *7/15 (RC), 9/10; 9/09; 5/09*
Implementation: *10/13/16; 8/25/15; 8/15; 1/1/11, 9/16/10*

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: Erenumab-aooe injection, subcutaneous

Date of Review: September 2018
Generic Name: erenumab-aooe

End Date of Literature Search: July 2018
Brand Name (Manufacturer): Aimovig™ (Amgen, Inc)
Dossier Received: yes

Research Questions:

1. What is the efficacy of erenumab compared to placebo or currently available therapy for preventative treatment of episodic or chronic migraines?
2. Is erenumab safe for the preventative treatment of episodic and chronic migraines?
3. Are there any subgroups (based on age, gender, ethnicity, comorbidities, disease duration or severity) that would particularly benefit or be harmed from treatment with erenumab?

Conclusions:

- There is moderate quality evidence from two phase 3 studies that adult patients with episodic migraine experienced 1 to 2 fewer monthly migraine days with both erenumab 70 mg and 140 mg compared to placebo over 24 weeks [-1.4 (95% confidence interval [CI], -1.9 to -0.9) and -1.9 (95% CI, -2.3 to -1.4), respectively] and with erenumab 70 mg versus placebo over 12 weeks [-1.0 (95% CI, -1.6 to -0.5)].[1,2,3] The clinical significance of this difference is unclear.
- There is moderate quality evidence from one phase 2 study that adult patients with chronic migraines given erenumab 70 mg or 140 mg experienced roughly 2 to 3 fewer monthly migraine days compared to placebo over 12 weeks [-2.5 (95% CI; -3.5 to -1.4) and -2.5 (95% CI; -3.5 to -1.4), respectively].[2,4] The clinical significance of this difference is unclear.
- There is insufficient evidence to evaluate the long term safety of erenumab. The safety population included a total of 2,184 patients. Mortality rates and serious adverse events were similar compared to placebo.[1-4] Adverse events more common with erenumab 70 mg and erenumab 140 mg versus placebo was injection site reaction (6% and 5% versus 3%, respectively) and viral infection (5% and 5% versus 3%, respectively).[1-4]
- There is insufficient evidence to compare the safety and efficacy of erenumab to any other FDA-approved migraine prophylaxis agents in specific subpopulations.[5]

Recommendations:

- Create a new class for calcitonin gene-related peptide (CGRP) antagonists.
- Recommend implementation of prior authorization criteria for CGRP antagonists (**Appendix 2**).

Author: David Engen, Pharm.D.

Background:
A migraine headache is a debilitating neurovascular brain disorder with a complex pathophysiology and often unpredictable onset.[6] Migraines are the principal cause of neurological disability and one of the most common diseases worldwide.[6] Some migraines are associated with visual or sensory symptoms referred to as an aura.[6] A migraine attack is often characterized by a unilateral, pulsating pain lasting hours to days along with photophobia, vertigo, nausea, and vomiting.[6] Although sensory, visual, speech, or motor aura symptoms may precede a migraine attack, this is not always the case.[6] Episodic migraines are those which occur less than 15 days per month with or without aura.[6] The definition of chronic migraine has recently been updated to include headache (migraine-like or tension-like) occurring on 15 or more days per month for more than 3 months, which, on at least 8 days per month, has migraine headache features.[6] Greater than 10% of the United States population experience migraines with attacks more frequent in adults 18-44 years of age.[7] Women are roughly 3 times more prone to migraines than men.[7, 8] Headaches have been identified as one of the major reasons for physician office encounters and account for roughly 3% emergency department (ED) visits.[7] Even with emergency treatment, roughly two-thirds of migraine patients released from the ED experience headache recurrence within 24 hours.[7] Migraines are highly disruptive to quality of life and productivity with the potential for significant impact on patient employment, interpersonal relationships and leisure activities.[9] Dangerous long-term cardiovascular health concerns of migraines include an increased risk for angina, hemorrhagic and ischemic stroke, venous thromboembolism, and myocardial infarction.[10] There are 556 unique Fee-for-Service Oregon Health Plan members who had paid medical claims for a migraine diagnosis between 7/1/17 and 12/31/17.

Migraines may be diagnosed and classified based on presence of aura, frequency of attack, symptoms and severity, as well as location of the pain.[6] The International Headache Society have published 2018 guidelines for the diagnosis of migraine which is summarized in **Table 1**.

Table 1: Comparison of Migraine without and with Aura[6]

Migraine without Aura	Migraine with Aura
At least 5 attacks lasting 4–72 hours (when untreated or unsuccessfully treated) fulfilling criteria below:	At least 2 attacks fulfilling criteria below:
Headache has at least two of the following four characteristics: 1. unilateral location 2. pulsating quality 3. moderate or severe pain intensity 4. aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)	At least three of the following six characteristics: 1. at least one aura symptom spreads gradually over 5 minutes 2. two or more aura symptoms occur in succession 3. each individual aura symptom lasts 5–60 minutes 4. at least one aura symptom is unilateral 5. at least one aura symptom is positive 6. the aura is accompanied, or followed within 60 minutes, by headache
During headache at least one of the following: 1. nausea and/or vomiting 2. photophobia and phonophobia	One or more of the following fully reversible aura symptoms: 1. visual (fortification spectrum) 2. sensory (radiating pin/needle disturbances, numbness) 3. speech and/or language 4. motor weakness 5. brainstem (vertigo, tinnitus, dysarthria, etc; no motor weakness) 6. retinal (monocular visual disturbance/scotomata/blindness)

A migraine attack may be triggered by substances in the diet (alcohol, tyramine- and nitrate-containing foods, monosodium glutamate, etc.), hormonal changes, stress, odors, altered sleep patterns, medication rebound, and weather changes.[11] There is evidence to suggest a genetic origin for the development of migraine headaches, particularly in migraines with aura.[12] Although the etiology of migraine headache is unclear, there are several messenger molecules that may be involved in the transmission of pain signaling including nitric oxide, 5-hydroxytryptamine (5-HT), and calcitonin gene-related peptide (CGRP).[12] CGRP is a 37-amino acid neuropeptide that exists in both the central and peripheral nervous systems as alpha/beta subtypes.[12] Studies have demonstrated that CGRP acts as a potent vasodilator within the intracranial and extracranial vessels and is believed to modulate vascular nociception in the CNS.[12] There are CGRP receptors throughout the cardiovascular and cerebrovascular tissue, kidneys, adrenal glands, and pancreas.[13] Although the role of CGRP in cardiovascular functioning is not well understood, there have been several recent studies which have investigated its effects in migraine pathophysiology and pain transmission.[14,15]

Several therapies approved by the Food and Drug Administration (FDA) are used for chronic migraine prophylaxis. The American Academy of Neurology and American Headache Society recommend that antiepileptic drugs (divalproex sodium/valproic acid, or topiramate) or beta blockers (propranolol, timolol, or metoprolol) be offered to patients for the prevention of episodic migraine (Level A:established efficacy based on 2 or more high quality trials).[16] The AAN also established onabotulinumtoxinA as an effective treatment option for patients with chronic migraine to decrease the number and severity of headaches (Level A) and as probably effective for improvement of health-related quality of life (Level B: probably effective based on 1 high quality or 2 moderate quality studies).[16] The AAN does not consider onabotulinumtoxinA to be effective for episodic migraine and recommends against its use in that patient population (Level A: ineffective based on at least 1 high quality or 2 moderate quality studies).[16] There are numerous preventative migraine therapies options that have been used successfully and more are currently under development.[17] A list of commonly prescribed FDA-approved treatments for migraine prophylaxis, their doses, and key safety information is provided in **Table 2**.

Table 2. Selected FDA-Approved Treatments for Migraine Prophylaxis (Modified table)[5]

Product Name	Dosing/Administration	Efficacy	Safety and Tolerability Concerns	Comments
Propranolol	20-80mg TID-QID	Treatment effect not in the label	Anaphylaxis, bradycardia	Bronchospasm and hypoglycemia in applicable populations
Timolol	10-15mg BID	Treatment effect not in the label	Anaphylaxis, bradycardia	Bronchospasm and hypoglycemia in applicable populations
Divalproex/sodium valproate	250-500mg BID	Treatment effect: 1.5 to 2.2-day reduction in monthly migraine days	Boxed warning for hepatotoxicity	Fetal risk of neural tube defects
Topiramate	50mg BID	Treatment effect: 1.0 to 1.3-day reduction in monthly migraine days	Paresthesias, weight loss	Fetal risk of cleft lip and palate
OnobotulinumtoxinA	Total dose 155 units divided across 7 muscles; administered every 12 weeks	Treatment effect: 1.4 to 2.3-day reduction in monthly headache days from baseline	Transient weakness may occur in muscles that are injected	Approved for chronic migraine only; administered intramuscularly by a physician

Abbreviations: BID = twice daily; TID = three times daily; QID – four times daily

One of the most important primary outcome measures used to evaluate effectiveness of migraine therapy is acute pain resolution.[18,19] However, there have also been several clinical tools used to document impact of migraine on patient disability and health-related quality of life. The Migraine Disability Assessment (MIDAS) is a five item questionnaire that was created to help patients track the number of days in the previous three months that a headache affected their

ability to carry out daily tasks.[20] No minimal clinically important difference (MCID) has been established for MIDAS. The Headache Impact Test (HIT-6) is a 6-question tool similar to MIDAS but each response is given an individual score and then tallied to assess overall impact.[20] The HIT-6 ranges from 36 to 78 points with higher scores indicative of greater impact.[20] A score of 60 or more on the HIT-6 is indicative that the migraine causes severe disability.[20] However, no clear MCID has been established for the HIT-6. The Migraine-Specific Quality of Life Questionnaire (MSQ) is a 14-item questionnaire which examines the extent of migraine impact on the patient's daily social and work-related activities, as well as their emotions.[20] The MSQ ranges from 0 to 100 with higher scores suggestive of a better quality of life.[20] A MCID for each of the MSQ domains established by previous trials has been reported to be -10.9 (role function-restrictive), -8.3 (role function-preventative), and -12.2 (emotional function).[20]

The migraine physical function impact dairy (MPFID) is a self-administered, 13-item instrument designed to assess how the patient's migraine affects everyday activities and the impact on physical impairment.[5,20] Patient responses are based on the previous 24 hours and scored on a 5-point scale (range 1 to 5, 5 = more negative impact).[5,20] Each MPFID domain score is converted and scaled to 100 points.[5,20] The scores for the 28-day period are the averaged and recorded.[5,20] The MPFID instrument has not been validated nor has a minimal clinically important change been identified.[5]

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Erenumab is a calcitonin gene-related peptide receptor antagonist indicated for the preventative treatment of migraine in adults. Erenumab was approved based on 3 studies (two phase 3 RCT and one phase 2 RCT) in patients with episodic or chronic migraine (**Table 5**). The primary outcome in the trials was mean monthly migraine days compared to baseline.[2] Erenumab therapy demonstrated reductions in monthly migraine days in all 3 trials versus placebo.[2]

In the first phase 3 trial (STRIVE; study 296; n=955), erenumab treatment was compared to placebo in the treatment of episodic migraine.[1,2,5] Baseline demographics, inclusion criteria, and exclusion criteria are reported in Table 5.[1,2,5] After a 4-week baseline period, patients were randomized 1:1:1 and entered into a 24-week double-blind active treatment phase to receive placebo, erenumab 70 mg, or erenumab 14 mg with a 12-week follow up.[1,2,5] The primary outcome studied was the change in mean number of monthly migraine days from baseline to the last 3 months of the double-blinded treatment period.[1,2,5] A key secondary endpoint was achievement of at least a 50% reduction from baseline in mean monthly migraine days. Additional secondary endpoints included changes from baseline in MPFID scores.[1,2,5] Patients used electronic health diaries to complete the MPFID for physical function and everyday activities and to record details about their migraine symptoms, pain severity, medication use, date and time of headaches.[1,2,5] A statistically significant mean reduction in monthly migraine days was observed in erenumab 70 mg and 140 mg versus placebo from baseline to the last 3 months of treatment.[1,2,5] The least squares mean difference (LSM) for erenumab 70 mg versus placebo was -1.4 (95% CI -1.9 to -0.9; p<0.001) and the LSM for erenumab 140 mg versus placebo was -1.9 (95% CI 2.3 to -1.4; p<0.001).[1,2,5] The key secondary endpoint of proportion of subjects with at least a 50% reduction in mean monthly migraine days from baseline to the last 3 months of treatment was higher in erenumab 70 mg and 140 mg versus placebo (43.3%, 50.0%, and 26.6% respectively; p<0.001; NNT=6 and 5).[1,2,5]

The second phase 3 trial (ARISE; study 297; n=577) had similar inclusion criteria,exclusion criteria, primary and secondary outcomes as the STRIVE trial.[2,3,5] However, patients only received erenumab 70 mg or placebo monthly for 12 weeks, followed by a 28-week open-label treatment phase of erenumab 70 mg monthly.[2,3,5] Changes from baseline in HIT-6, MIDAS, and MSQ scores were additional exploratory endpoints.[2,3,5] The LSM change in MMDs favored erenumab over placebo (-2.9 vs. -1.8, respectively) with a LSM difference of -1.0 (95% CI -1.6 to -0.5, p<0.001) days.[2,3,5] A higher proportion of erenumab patients achieved

a 50% or greater reduction in MMDs compared to placebo (39.7% vs. 29.5%, respectively) with an adjusted odds ratio (OR) of 1.6 (95% CI 1.1 to 2.3, p = 0.010).[2,3,5] Other secondary patient-reported outcomes of potential relevance were not statistically significant.[2,3,5]

Study 295 (n=667) was a phase 2 RCT in chronic migraine patients.[3,4,5] Patients were randomized 3:2:2 to placebo, edaravone 70 mg, and edaravone 140 mg.[3,4,5] Patient demographics and outcomes were similar to STRIVE and ARISE with a baseline MMD of 18 days among all groups.[3,4,5]A statistically significant greater mean MMD reduction was noted for both erenumab treatment doses versus placebo with a LSM difference of -2.46 (95% CI -3.52 to -1.39; p< 0.001) for erenumab 70 mg versus placebo and -2.45 (95% CI -3.52 to -1.38; p<0.001) for erenumab 140 mg versus placebo.[3,4,5] The proportion of subjects with a 50% or greater reduction in MMD from baseline to the last 4 weeks of the treatment phase was 23.5%, 39.9% (NNT=7), and 41.2% (NNT=6) for placebo, erenumab 70 mg and erenumab 140 mg, respectively (p<0.001 for both erenumab doses).[3,4,5]

Limitations

Limitations to this evidence include an inability to detect effects in the male population given the low percentage of male participants. Physical function and ability to perform daily activities was measured with the MPFID tool which has not been widely recognized as a validated form of assessment. There may be little value in statistically significant MPFID results without an established minimal clinically important difference value.

A migraine day could be counted if a patient took an acute migraine-specific drug to treat a headache regardless of headache duration or pain symptoms. Given the subjective nature of the definition of a migraine day, the clinical significance of 1 to 2 fewer migraine days per month is uncertain. The 50% responder rate was based on monthly migraine reduction compared to baseline, but the baseline monthly migraine days were initially relatively low which indicates a population with mild disease. Therefore, it is unclear whether or not erenumab would be effective in moderate to severe disease. Only study 295 evaluated the use of erenumab in treating chronic migraine.

Many oral agents are FDA-approved for chronic migraine therapy but patient adherence has typically been poor. Treatment effects in patients who failed more than 2 migraine preventative medications are unknown due to their exclusion from trials. Erenumab is given subcutaneously which is may be a less preferred route of administration compared to oral agents for many patients. The primary authors for phase 3 studies are also creators of the IHS guidelines with multiple grants, consultancy and industry support from major pharmaceutical manufacturers including, but not limited to, Amgen. Head-to-head studies may be needed to evaluate erenumab's place in therapy.

Clinical Safety:

Side effects observed in clinical trials which were more common with erenumab than placebo include infection from any cause, injection site reaction, viral infection, constipation, and cramps/muscle spasms (**Table 3**).[2,5] No serious adverse reactions occurred in more than 1% of patients or more frequently than placebo.[2,5] Overall discontinuations due to adverse reactions was low in clinical trials (1.2, 1.7, and 2.4% for placebo, erenumab 70 mg, and erenumab 140 mg, respectively).[2,5]

Table 3: Adverse Drug Reactions Which Occurred ≥2% More Commonly in Erenumab--Treated Patients than Placebo-Treated Patients[2]

Adverse Reactions	Placebo (n=890) N	Erenumab 70 mg (n=787) N	Erenumab 140 mg (n=507) N
Infection, all	25%	25%	27%
Injection site reaction	3%	6%	5%
Infection, viral	3%	5%	5%
Constipation	1%	1%	4%
Cramps, muscle spasms	0%	0%	2%

Theoretical concerns of impaired vasodilation from CGRP inhibition include worsening ischemia in patients with angina, increased thrombotic events in at-risk individuals, and a worsening of Raynaud's phenomenon symptoms.[5] Patients over age 65 with higher cardiovascular risk and those with existing cardiovascular disease were not recruited in the clinical trials.[5] The FDA concluded that nonclinical data did not raise substantial concern about cardiovascular risk, and therefore, no post-market safety studies were required for erenumab.[5] Safety of erenumab in pregnancy and breastfeeding mothers as well as long-term risks of CGRP blockade beyond 24 weeks remain unknown.[5]

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Migraine frequency
2) Migraine intensity
3) Migraine duration
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Change from baseline in migraine days per month

Table 4: Pharmacology and Pharmacokinetic Properties.[2,5,21]

Parameter	
Mechanism of Action	A human monoclonal antibody that binds to the CGRP receptor and antagonizes CGRP receptor function
Bioavailability	Subcutaneous: 82%
Distribution and Protein Binding	3.86 L
Elimination	Degradation by reticuloendothelial cells and breakdown within lysosomes of cells with the CGRP receptor
Half-Life	28 days
Metabolism	Catabolism into amino acids

Abbreviations: CGRP = calcitonin gene-related peptide; L = liter

Table 5. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Goadsby, et al (Study 296 - STRIVE)[1,2,5] Phase 3 RCT, MC, DB, PC, PG study of patients with EM	1. Placebo 2. Erenumab 70 mg 3. Erenumab 140 mg Given SQ once every 4 weeks x24 weeks	Demographics: - Mean Age: 41 (range: 18-65) - Age <56: 89% - Female: 85% - Geographic region North America: 50% - Race: White: 89% Black: 7% - Other: 4% - BMI: 27+/-6 kg/m^2 - Disease duration: 20 years - Mean migraine days per month: 8.3 Key Inclusion Criteria: - History of migraine for ≥12 months - Migraine frequency of 4 to 14 days/month with <15 headache days/month Key Exclusion Criteria: - Older than 50 years old at migraine onset; - Hx of cluster HA or hemiplegic migraine - No therapeutic response to more than 2 preventive tx categories; - Recent use of ergots or triptans, simple analgesics, or opioid or butalbital-containing analgesics - Recent use of migraine preventive medications or prior use botulinum	ITT: 1. 319 2. 317 3. 319 PP: 1. 316 2. 312 3. 318 Attrition: 1. 3 (1%) 2. 5 (2%) 3. 1 (<1%)	Primary Endpoint: Change from baseline in migraine days per month 1. -1.8 2. -3.2 3. -3.7 1 vs. 2: LSMD -1.4 (95% CI, -1.9 to -0.9); p <0.001 1 vs. 3: LSMD -1.9 (95% CI, -2.3 to -1.4); p <0.001 Key Secondary Endpoints: Proportion with ≥ 50% reduction in monthly migraine days 1. 26.6% 2. 43.3% 3. 50.0% 1 vs. 2. OR 2.1 (95% CI, 1.5 to 3.0); p-value <0.001 1 vs. 3. OR 2.8 (95% CI, 2.0 to 3.9); p-value <0.01 Change from Baseline in Mean Monthly Average Impact on Everyday Activities Score (MPFID) – Adjusted FDA analysis 1. -3.3 2. -5.5 3. -5.9 1 vs. 2. LSMD -2.2 (95% CI, -3.3 to -1.2); p<0.001 1. vs. 3. LSMD -2.6 (95% CI, -3.6 to -1.5); p<0.001 Change from Baseline in Mean Monthly Average MPFID Physical Impairment Domain Scores – Adjusted FDA analysis 1. -2.4	NA NA 16.7%/6 23.4%/5 NA NA NA	Outcome: Overall percent of patients reporting at least 1 adverse event: 1. 63% 2. 57% 3. 56% SAEs 1. 7 (2%) 2. 8 (3%) 3. 6 (2%) Discontinuation from Adverse Events 1. 8 (3%) 2. 7 (2%) 3. 7 (2%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Subjects given ID numbers with drug allocation centrally determined by Interactive Response Technology; patients, site personnel, trial sponsors blinded to treatment assignments Performance Bias: Unclear. Subjects and investigators blinded but no details provided Detection Bias: Unclear. Subjective patient-reported outcomes collected, tallied, and converted by unmentioned parties Attrition Bias: Low. Full analysis in final protocol included all patients who underwent randomization Reporting Bias: High. Patients completed diary entries over prior 24 hours with no safeguards against information gaps or overlap; original protocol collected PROs in eDiary for secondary endpoints (MIDAS, MSQ, HIT-6, etc) were omitted from the published draft due to non-significant results of study 297 (FDA allowed change); MPFID scores transformed into 100 point scale without methodology disclosed Other Bias: Unclear. Main author an IHS Committee member who was also an author for the 2018 *Guidelines for controlled trials of preventive treatment of chronic migraine in adults* published after the study **Applicability**: Patient: Excluded patients over age 65 and with CVD; Effects of CGRP receptor blockade in CVD patients with ischemia unknown could theoretically interfere with cardioprotective vasodilatory mechanisms that occur during acute ischemia; females were likely over-represented in a ratio of 6:1; percentage of blacks and Hispanics lower than expected; no concurrent migraine prophylactic medication allowed Intervention: Appropriate FDA-approved dose; subcutaneous administration

		toxin injections in the head and/or neck region; - Recent MI, stroke, TIAs, unstable angina, CAB surgery, or other revascularization procedures		2. -4.2 3. -4.8 1 vs. 2. 1.9 (95% CI, -3.0 to -0.8); p-value<0.001 1 vs. 3. 2.4 (95% CI, -3.5 to -1.4); p-value<0.001	NA			Comparator: Study excluded most current FDA-approved agents and standards of care for episodic and chronic migraine prophylaxis Outcomes: Migraine day definition subject to wide variation and interpretation; migraine duration of 30 minutes or greater included in the calculation of the primary endpoint; MPFID not validated Setting: 121 centers in North America and Europe (50% participants from Europe and Turkey)
2. Dodick, et al (Study 297-ARISE) [2,3,5] Phase 3, MC, randomized, DB, PC, PG study of patients with EM	1. Placebo 2. Erenumab 70 mg Dosed SQ every 4 weeks x12 weeks	Demographics: - Mean Age: 42 - Female: 85% - Geographic region: United States 59% - White: 90% - BMI: 27.4 - Disease duration: 21 years - Migraine days per month: 8.2 Key Inclusion Criteria: - Adults 18 to 65 years old - History of migraine with or without aura for at least 12 months - At least 4 to < 15 migraine days/month with < 15 HA days/month Key Exclusion Criteria: - See STRIVE	ITT: 1. 291 2. 286 PP: 1. 288 2. 282 Attrition: 1. 3 (1%) 2. 4 (1%)	Primary Endpoint: Change from baseline in migraine days per month 1. -1.8 2. -2.9 LSM difference -1.0 (95% CI, -1.6 to -0.5); p <0.001 Key Secondary Endpoints: Proportion of patients with ≥ 50% reduction in monthly migraine days 1. 29.5% 2. 39.7% OR 1.6 (95% CI; 1.1 to 2.3) p = 0.010	NA 10.2%/10	Outcome: Discontinuation of study drug: 1. 1 (0.3%) 2. 5 (1.8%) Common adverse events: URTI 1. 14 (4.8%) 2. 18 (6.4%) Injection site pain 1. 12 (4.2%) 2. 17 (6.0%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomization based on computer-generated schedule created by sponsor before study began and centrally executed with interactive response system; groups well balanced at baseline Performance Bias: Low. Patients, site personnel, and sponsor blinded to treatment groups; identical packaging, size, and color of drug and placebo Detection Bias: Unclear. Independent data monitoring committee reviewed and made recommendations regarding the safety of study participants throughout double blind treatment phase but no details provided Attrition Bias: Low. 570/577 patients analyzed for primary efficacy; 522 included in per protocol Reporting Bias: Unclear. Monthly patient counts of e-diary entries for each group was ~95%; Manufacturer analyzed data and provided support/funding for medical writing Other Bias: Unclear. Main author sits on IHS Committee that created *2018 Guidelines for controlled trials of preventive treatment of chronic migraine in adults* **Applicability**: Patient: Mostly white females studied; excluded patients resistant to >2 migraine preventative treatment; concomitant acute migraine treatment medication allowed Intervention: FDA-approved erenumab 140 mg was not studied; subcutaneous administration Comparator: Placebo appropriate for efficacy but study excluded most current alternative FDA-approved agents and standards of care for episodic and chronic migraine prophylaxis

								Outcomes: Migraine day definition (mean monthly change and proportion of subjects with ≥ 50% reduction) as endpoints subject to wide variation and interpretation; migraine duration of 30 minutes or greater included in the calculation of the primary endpoint; MPFID not validated Setting: 69 centers in Denmark, France, Greece, Portugal, Russian Federation, Spain, Switzerland, and the U.S.
3. Tepper, et al (Study 295)[2,4,5] Phase 2, randomized, DB, PC study of CM patients	1. placebo 2. erenumab 70 mg 3. erenumab 140 mg Dosed SQ every 4 weeks x12weeks	Demographics: -Mean Age: 42 -Female: 83% -Geographic region: North America: 47% -White: 94% -BMI: 26 -Disease duration: 21 years -Migraine days per month: 18 Key Inclusion Criteria: - Hx of 15 or more HA days/month, with 8 or more migraine days/month Key Exclusion Criteria: - Chronic migraine where the patient was not experiencing any pain free periods - Opioid use for >12 days during three months prior to screening - Butalbital use >6 days during the 3 months prior - No therapeutic response in prophylaxis of migraine after an adequate trial of > 3 prophylactic medications - Use of a prohibited migraine prophylactic medication within two months prior	ITT: 1. 286 2. 191 3. 190 PP: 1. 281 2. 188 3. 187 Attrition: 1. 5 (2%) 2. 3 (2%) 3. 3 (2%)	Primary Endpoint: Change from baseline in migraine days per month 1. -4.2 2. -6.6 3. -6.6 1 vs. 2: LSMD -2.5 (95% CI; -3.5 to -1.4); p-value <0.001 1 vs. 3: LSMD -2.5 (95% CI; -3.5 to -1.4); p-value <0.001 Key Secondary Endpoints: Proportion of patients with ≥50% reduction in monthly migraine days from baseline 1. 23.5% 2. 39.9% 3. 41.2% Adjusted odds ratio: 1 vs. 2: 2.2 (95% CI; 1.5 to 3.3) p-value <0.001 1 vs. 3: 2.3 (95% CI; 1.6 to 3.5) p-value <0.001	NA NA 16.4%/7 17.7%/6	Outcome: Overall percent of patients reporting at least 1 adverse event 1. 39% 2. 44% 3. 47% Overall adverse events leading to treatment discontinuation: 1. 1% 2. 0% 3. 1%	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Sponsor-generated randomization sequence executed by IVR; patients, sponsor, and study personnel all masked to treatment assignment; baseline characteristics similar among groups Performance Bias: Low. Placebo and active drug presented in identical vials, storage containers, etc Detection Bias: Low. Analysis included all patients randomized to their respective treatment categories Attrition Bias: Low. Minimal dropouts; missing data unlikely to influence results Reporting Bias: Unclear. Electronic diaries used to record migraine incidence, severity, and symptoms migraine; if at least 14 days of 28-day interval was recorded in e-diary, then the monthly measurement was prorated to 28-day or computed as average from the available observed days of data Other Bias: High. One of main authors also on IHS Committee who created *2018 Guidelines for controlled trials of preventive treatment of chronic migraine in adults*; study sponsor developed study protocol with investigators and also managed study sites, performed the statistical analysis, and funded support of medical writers **Applicability**: Patient: Excluded patients taking concurrent migraine prophylaxis medications; patients with diagnosis of chronic migraine due to medication overuse of triptans, ergots, and other analgesics were also excluded Intervention: Both FDA-approved doses of erenumab studied; subcutaneous administration

		- Patients with diagnosis or history of pertinent select comorbid neurologic or mental health conditions, cardiovascular issues, or substance abuse - Body mass index >40 kg/m2						Comparator: Placebo control appropriate to establish safety and efficacy Outcomes: Primary endpoint was measured in the last four weeks of the double-blind treatment period- Setting: 69 centers in North America (US and Canada) and Europe (Czech Republic, Denmark, Germany, Finland, Norway, Poland, Sweden, and United Kingdom).
Abbreviations: ARR = absolute risk reduction; CAB = Coronary Artery Bypass; CI = confidence interval; CM = chronic migraine; CVD = cardiovascular disease; EM = episodic migraine; HA = headache; HIT-6 = Headache Impact Test; Hx = history; IHS = International Headache Society; ITT = intention to treat; IVR = interactive voice response; LSMD = least squares mean difference; mITT = modified intention to treat; MI = myocardial infarction; MIDAS = Migraine Disability Assessment; MPFID= migraine physical function impact dairy; MSQ = Migraine-Specific Quality of Life Questionnaire; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; OR = odds ratio; PP = per protocol; PG = parallel group; PROs = patient-reported outcomes; TIA = transient ischemic attack; SAE = serious adverse events; SQ = subcutaneously; Tx = treatment								

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Appendix 1: Prescribing Information Highlights

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

AIMOVIG™ (erenumab-aooe) injection, for subcutaneous use
Initial U.S. Approval: 2018

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

AIMOVIG is a calcitonin gene-related peptide receptor antagonist indicated for the preventive treatment of migraine in adults (1)

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

- For subcutaneous use only (2.1, 2.2)
- Recommended dosage is 70 mg once monthly; some patients may benefit from a dosage of 140 mg once monthly (2.1)
- The 140 mg dose is administered once monthly as two consecutive injections of 70 mg each (2.1)
- The needle shield within the white cap of the prefilled autoinjector and the gray needle cap of the prefilled syringe contain dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex (2.2)
- Administer in the abdomen, thigh, or upper arm subcutaneously (2.2)
- See Dosage and Administration for important administration instructions (2.2)

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

- Injection: 70 mg/mL solution in a single-dose prefilled SureClick® autoinjector (3)
- Injection: 70 mg/mL solution in a single-dose prefilled syringe (3)

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

None (4)

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

The most common adverse reactions in AIMOVIG clinical studies (occurring in at least 3% of treated patients and more often than placebo) are injection site reactions and constipation (6.1)

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

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

Revised: 5/2018

Calcitonin Gene-Related Peptide (CGRP) antagonists

Goal(s):
- Promote safe use of CGRP inhibitors in adult patients
- Promote use that is consistent with medical evidence and product labeling

Length of Authorization:
- Initial: Up to 3 months
- Renewal: Up to 12 months

Requires PA:
- All calcitonin gene-related peptide (CGRP) antagonists

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA-approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Is this a request for renewal of a previously approved Fee-For-Service prior authorization of a CGRP antagonist for management of migraine headache?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #5

Approval Criteria		
5. Is there documentation that the patient has experienced 4 or more migraine days in the previous month?	**Yes:** Document migraine days per month _____ Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Has the patient failed an adequate trial (≥6 weeks with a documented adherence of ≥80%) of an FDA-approved migraine prophylaxis medication from each of the following classes: Beta-blockers: propranolol; timolol Anticonvulsants: divalproex/sodium valproate; topiramate OR Does the patient have a documented intolerance, FDA-labeled contraindication, or hypersensitivity to each of the above migraine prophylaxis agents?	**Yes:** Document agents used and dates _____ _____ Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Has the patient received an injection with botulinum toxin for headache treatment once in the previous 2 months?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #8
8. Is the medication being prescribed by or in consultation with a neurologist or pain specialist?	**Yes:** Approve for 3 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
Has the patient experienced a documented positive response to therapy, as demonstrated by a reduction in migraine headache frequency and/or intensity from baseline?	**Yes: Document response** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

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: Pegvaliase-pqpz injection, subcutaneous

Date of Review: September 2018
Generic Name: pegvaliase-pqpz

End Date of Literature Search: 06/27/2018
Brand Name (Manufacturer): Palynziq™ (BioMarin Pharmaceutical Inc.)
Dossier Received: yes

Research Questions:

1. What is the efficacy of pegvaliase compared to placebo or currently available treatments for phenylketonuria (PKU)?
2. Is pegvaliase safe for the treatment of PKU?
3. Are there any subgroups (based on age, gender, ethnicity, comorbidities, disease duration or severity) that would particularly benefit or be harmed from treatment with pegvaliase?

Conclusions:

- Efficacy evidence for pegvaliase comes from one discontinuation trial (n=86) with high risk of selection bias in which patients were randomized to either discontinue or maintain treatment with pegvaliase.[1]
- Low quality of evidence found a statistically significant difference in the increase of blood phenylalanine levels in PKU patients stable on pegvaliase from the beginning of the discontinuation trial to week 8 in the pooled pegvaliase group (26.5 µmol/L) compared to the 20 mg/day and 40 mg/day placebo groups (949.8 µmol/L and 664.8 µmol/L, respectively; p=0.0001 for both groups vs. pooled pegvaliase).[1] The pooled pegvaliase group remained at near the same levels as the beginning of the randomized discontinuation trial (<600 µmol/L) while placebo groups experienced an increase in levels to values higher than the American College of Medical Genetics and Genomics (ACMG) guideline-recommended lifetime phenylalanine goal of 120-360 µmol/L and also higher than the United States Food and Drug Administration (FDA)-approved PKU indication for initiation of pegvaliase (>600 µmol/L on existing management).[1-3]
- There is insufficient evidence to determine differences in neuropsychiatric or neurocognitive symptoms as measured by the Attention Deficit Hyperactivity Disorder Rating Scale IV inattention subscale (ADHD RS-IV IA) and Profile of Mood States (POMS) scores including POMS, PKU-POMS, and PKU-POMS confusion subscale score in patients treated with pegvaliase versus placebo.[1] Results were not statistically significant for these outcomes.[1]
- Safety concerns with pegvaliase include anaphylaxis, which occurred in 9% (n=26) of patients treated with pegvaliase in the FDA safety analysis (n=285).[3] Pegvaliase has a boxed warning regarding anaphylaxis, is only available through a Risk Evaluation and Mitigation Strategy (REMS) program, and requires that patients prescribed pegvaliase are also prescribed auto-injectable epinephrine.[3]
- There is insufficient direct evidence to determine comparative efficacy of pegvaliase and sapropterin for PKU.
- There is insufficient evidence to determine if any subgroups would particularly benefit or be harmed from treatment with pegvaliase.

Recommendations:

- Implement prior authorization criteria for pegvaliase (**Appendix 2**).

Background:

Phenylketonuria (PKU) is an autosomal recessive disorder caused by an error in amino acid metabolism.[4] Patients with PKU have a deficiency of phenylalanine hydroxylase, which results in increased levels of phenylalanine in the blood and brain.[5] PKU has an incidence of 1 in 15,000 live births in the United States and in the Oregon Health Plan (OHP) fee-for-service (FFS) population there are over 200 patients with diagnoses of PKU.[5] While newborn PKU screening is recommended by the U.S. Preventive Services Task Force and rarely untreated, if undiagnosed or untreated PKU symptoms include severe mental retardation, developmental delays, epilepsy, behavioral problems, eczema-like dermatologic problems, and a mousy odor (due to the buildup of phenylalanine).[5,6] Once hyperphenylalaninemia is identified in a newborn screening, plasma amino acid analysis is completed to confirm elevated phenylalanine concentrations and then additional tests are completed to differentiate PKU from other causes of hyperphenylalaninemia.[2] Genotyping is then completed to determine metabolic phenotype and extent of recommended dietary phenylalanine restriction as well as the likelihood of response to tetrahydrobiopterin (BH4; sapropterin) supplementation.[2]

The 2014 American College of Medical Genetics and Genomics (ACMG) PKU guidelines recommend treatment initiation for patients with phenylalanine levels greater than 360 µmol/L.[2] However, some treatment centers may not initiate treatment unless levels are greater than 600 µmol/L given mixed evidence of outcomes for untreated patients with levels between 360 and 600 µmol/L.[2] Treatment initiation is recommended upon diagnosis, preferably within the first week of life, with the goal of achieving control in the first 2 weeks of life.[2] Initial treatment usually includes excluding phenylalanine from the diet until within the goal range, and implementation of a phenylalanine-restricted diet afterwards.[2] Relaxation of phenylalanine control later in life and subsequent buildup of phenylalanine can result in neurocognitive and psychiatric symptoms, and therefore the goal of treatment is to maintain lifelong blood phenylalanine levels of 120-360 µmol/L.[2] While lower than the normal range, levels of 60-120 µmol/L are not considered too low based on available evidence, but phenylalanine levels less than 30 µmol/L should be avoided.[2] Symptom improvement usually occurs with a reduction of phenylalanine levels.[2] Recommended blood phenylalanine monitoring frequencies based on age are listed in **Table 1**.[2]

Table 1. Recommended Frequency of Blood Phenylalanine Levels Based on Patient Age[2]

Age	Frequency of Monitoring
Newly diagnosed infants	Frequently until levels are stabilized
Less than 1 year	At least weekly
1-12 years	Biweekly to monthly
Adolescents and adults with stable levels	Monthly

Dietary restriction of phenylalanine is the mainstay of therapy.[2] Foods which contain phenylalanine and should be restricted include meat, fish, milk, cheese, eggs, nuts, flour, soy, and drinks with aspartame.[4,5] Medical food products containing phenylalanine-free amino acid mixtures are also recommended to meet established dietary requirements.[2,5]

Sapropterin dihydrochloride (Kuvan®) was approved in 2007 by the U.S. Food and Drug Administration (FDA) to lower blood phenylalanine levels in patients with hyperphenylalaninemia due to BH4-responsive PKU in conjunction with a phenylalanine-restricted diet.[7] Sapropterin works by activating residual phenylalanine hydroxylase activity to improve the metabolism of phenylalanine, and therefore decrease phenylalanine levels.[7] It was the first medication indicated for PKU at

the time of its approval. Around 25-50% of patients with PKU are responsive to sapropterin, and genotyping may be predictive of response.[2,7] In sapropterin clinical trials, response was defined as at least a 30% decrease in blood phenylalanine levels from baseline.[7]

Large neutral amino acids (LNAA) may also be used for PKU therapy, but larger trials are necessary to determine safety and efficacy.[2] LNAAs are available in several formulations and are classified as a medical food, which are not reviewed by the FDA.[8]

Pegvaliase-pqpz (Palynziq™) is a recently FDA-approved medication indicated to reduce blood phenylalanine concentrations in adult patients with phenylketonuria who have uncontrolled blood phenylalanine concentrations greater than 600 µmol/L on existing management.[3]

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

Clinical Efficacy:
Pegvaliase is a phenylalanine-metabolizing enzyme approved by the FDA in May 2018 indicated to reduce blood phenylalanine concentrations in adult patients with PKU who have uncontrolled phenylalanine concentrations greater than 600 µmol/L on existing management.[3] Approval was based on two phase 3 trials, PRISM-1 and PRISM-2.[1,9,10]

PRISM-1 was an open-label, parallel group phase 3 study in which patients were administered with an induction, titration, and maintenance dosing regimen of either pegvaliase 20 mg/day or 40 mg/day.[9] The primary outcome of PRISM-1 was focused on safety which will not be discussed in this section but is included in the FDA safety analysis.[3,9] If a patient was unable to titrate to or maintain their randomized pegvaliase 20 mg/day or 40 mg/day dose in PRISM-1 (n=16), they were enrolled into PRISM-2 Part 4 for the open-label extension period and were not included in PRISM-2 Parts 1-3 described below.[1,9] Another 54 patients also discontinued pegvaliase early in PRISM-1 due to adverse events (n=29), withdrawal by patient, physician decision, pregnancy, protocol deviation, loss to follow-up, or another reason and did not enter PRISM-2 at all.[9]

PRISM-2 was a four-part phase 3 clinical study of pegvaliase.[1,9] Part 1 was an open-label continuation of PRISM-1 where patients remained on their maintenance 20 mg/day or 40 mg/day regimen of pegvaliase and eligibility to enter Part 2 was assessed.[9] Part 2 of PRISM-2 was a double-blind, placebo-controlled, randomized discontinuation trial in which patients remained on their 20 mg/day or 40 mg/day regimen of pegvaliase from Part 1 or were randomized to a matching placebo.[9] In Part 3, any patients randomized to placebo returned to their 20 mg/day or 40 mg/day regimen of pegvaliase from Part 1 for pharmacodynamic and pharmacokinetic analyses.[9] Finally, Part 4 was an open-label extension period to assess long term outcomes.[9] The focus of the FDA efficacy review was on PRISM-2 Part 2, which is described and evaluated below in **Table 4**, as it was the only placebo-controlled period of the phase 3 trials.[1,10]

The randomized discontinuation trial in PRISM-2 Part 2 enrolled patients who were stable on pegvaliase 20 mg/day or 40 mg/day from PRISM-1 who also achieved a blood phenylalanine reduction of at least 20% (from mean of 2 consecutive blood phenylalanine assessments) from treatment-naïve baseline at the time of discontinuation trial entry.[1] Included patients (n=86) were 18 years of age and older with PKU.[1] Prior to PRISM-1, patients were required to discontinue any sapropterin or large neutral amino acids and any neuropsychiatric medications were required to be at stable doses.[1] Patients were provided with epinephrine injectors for use in case of acute systemic hypersensitivity events.[1] A statistically significant difference was found in the primary endpoint of change in blood phenylalanine levels at week 8 with the pooled pegvaliase group (26.5 µmol/L) compared to the 20 mg/day and 40 mg/day placebo groups (949.8

µmol/L and 664.8 µmol/L, respectively; p=0.0001 for both groups vs. pooled pegvaliase).[1] The pooled pegvaliase group remained at near the same levels as the beginning of the randomized discontinuation trial (<600 µmol/L) while placebo groups experienced an increase in levels to values higher than the ACMG guideline-recommended lifetime phenylalanine goal level of 120-360 µmol/L and also higher than the United States Food and Drug Administration (FDA)-approved PKU indication for initiation of pegvaliase (>600 µmol/L on existing management).[1-3]

Secondary endpoints for the trial included neuropsychiatric or neurocognitive symptoms as measured by the Attention Deficit Hyperactivity Disorder Rating Scale IV inattention subscale (ADHD RS-IV IA) and Profile of Mood States (POMS) scores.[1] The ADHD-RS-IV IA was administered by investigators (scale 0-27; higher scores indicate greater impairment) while the POMS instrument was self-administered by study participants (scale -32 to 200; higher scores indicate greater mood symptoms).[1] No statistically significant differences were found in these secondary endpoints or additional PKU-specific POMS scales, PKU-POMS and PKU-POMS confusion subscale score.[1] The FDA clinical review noted that the lack of significant results may be due to the small sample size and short 8 week duration.[10] There may also be limitations in patient-reporting of symptoms in the scales used due to self-awareness concerns based on phenylalanine control.[1]

PRISM-1 and PRISM-2 Combined Analysis

A combined analysis of PRISM-1 and PRISM-2 reported that that within 24 months, 64.8% of patients treated with pegvaliase achieved blood phenylalanine levels of 600 µmol/L or lower, 60.7% achieved levels of 360 µmol/L or lower, and 51.2% achieved levels of 120 µmol/L or lower.[9] Statistical significance of these results was not reported.[9] Levels of 120-360 µmol/L are clinically significant as this is the ACMG guideline-recommended lifetime goal for phenylalanine levels.[2]

An analysis was also completed by the FDA to determine how long it took patients with a pre-treatment blood phenylalanine level of over 600 µmol/L to achieve a first response, as defined by at least a 20% reduction in blood phenylalanine concentration from pre-treatment baseline or a blood phenylalanine level of 600 µmol/L or lower.[10] Of 118 patients who received a dose of pegvaliase 20 mg/day, 70% (n=81) reached their first response between 4 and 24 weeks of 20 mg/day treatment.[10] Of the 118 patients, 25 later escalated their dose to 40 mg/day and of those, 56% achieved their first response after 4-16 weeks of 40 mg/day treatment.[10]

Limitations

Both PRISM-1 and PRISM-2 were funded by BioMarin Pharmaceutical Inc., the manufacturer of pegvaliase.[1,9] Limitations of PRISM-2 Part 2 include a high overall attrition rate (16.3%) in a trial of short duration (8 weeks).[1] Additionally, this trial does not provide data on the maximum blood phenylalanine level lowering ability of pegvaliase as patients treated in Part 2 had already been stable on 20 mg/day or 40 mg/day of pegvaliase.[1] Furthermore, there is a risk of selection bias due to the structure of the trials in that patients who could not titrate to or maintain a maintenance dose of pegvaliase were not included in the PRISM-2 Part 2 discontinuation trial.[9] Patients who did not achieve a blood phenylalanine reduction of at least 20% (from mean of 2 consecutive blood phenylalanine assessments) from treatment-naïve baseline at the time of randomized discontinuation trial entry were also not included in PRISM-2 Part 2, adding to the risk of selection bias.[9] Efficacy of pegvaliase in combination with or compared to sapropterin remains unknown as patients were required to discontinue sapropterin use prior to pegvaliase trials.[1,9] Efficacy and safety of pegvaliase in pediatric patients is also unknown as only patients 18 years and older were included in the PRISM-1 and PRISM-2 trials, which is significant as PKU is diagnosed and treated early in life.[1,3,9] Long-term efficacy of pegvaliase remains unclear as the randomized discontinuation trial was limited to 8 weeks.[1] However, long-term extension trials are ongoing.[9]

Dietary Restriction of Phenylalanine

FDA labeling recommends monitoring of dietary protein and phenylalanine intake but does not specifically require monitoring or dietary restrictions during pegvaliase treatment.[3] Patients should be counseled on how to adjust their dietary intake of phenylalanine if needed based on their blood phenylalanine levels.[3]

Clinical Safety:
The most common adverse reactions (≥20%) with pegvaliase treatment were injection site reactions, arthralgia, hypersensitivity reactions, headache, generalized skin reactions lasting at least 14 days, pruritus, nausea, abdominal pain, oropharyngeal pain, vomiting, cough, diarrhea, and fatigue.[3] The incidence of most common adverse reactions is summarized in **Table 2**.[3] During the induction/titration/maintenance regimen of trials, 11% of patients (n=31) discontinued treatment due to adverse reactions, with the most common reason being hypersensitivity reactions (6% of patients; 3% anaphylaxis).[3] Arthralgia and hypersensitivity reactions were the most common events leading to dose reduction (14% and 9% of patients, respectively).[3]

Table 2. Adverse Reactions Reported in at Least 20% of PKU Patients Treated with Pegvaliase in Either the Induction/Titration Phase or Maintenance Phase[3]

Adverse Reaction	Induction/Titration Phase (N=285), %	Maintenance Phase (N=223); %
Injection site reactions	88%	72%
Arthralgia	74%	61%
Hypersensitivity reactions	53%	61%
Headache	35%	50%
Generalized skin reaction lasting ≥14 days	21%	37%
Pruritis	20%	24%
Nausea	18%	26%
Abdominal pain	14%	25%
Oropharyngeal pain	13%	23%
Fatigue	13%	22%
Vomiting	13%	26%
Cough	9%	22%
Diarrhea	9%	22%

FDA-approved labeling for pegvaliase includes a boxed warning for risk of anaphylaxis as it has been reported after administration and may occur at any time.[3] In clinical trials, 9% of patients (n=26) experienced anaphylaxis, with a total of 37 anaphylaxis episodes.[3] Anaphylaxis most commonly occurred within 1 hour of injection (84%; 28/37 episodes) but delayed episodes also occurred up to 48 hours after administration of pegvaliase.[3] A majority of episodes occurred during the first year of pegvaliase use (78%; 29/37 episodes), but cases also occurred up to 2.3 years into treatment.[3] Management of anaphylaxis included auto-injectable epinephrine (54%), corticosteroids (54%), antihistamines (51%), and oxygen (5%).[3] Of those who experienced anaphylaxis, 18 (69%) were re-challenged with pegvaliase treatment and 28% of those patients (n=5) had recurrence of anaphylaxis.[3] It is recommended to administer the initial dose of pegvaliase under the supervision of a healthcare provider equipped to manage anaphylaxis with observation of the patient for at least an hour after injection.[3] Additionally, auto-injectable epinephrine should be prescribed concurrently with pegvaliase. Due to these anaphylaxis concerns, pegvaliase is only available through a REMS program.[3]

Other hypersensitivity reactions also occurred in 69% of pegvaliase-treated patients. Rates were highest in the induction and titration phases (4.5 episodes/person-year; 50% of patients with at least 1 adverse reaction) and decreased in the maintenance phase (1.5 episodes/person-year; 57% of patients

with at least 1 adverse reaction).[3] The FDA clinical review noted hypersensitivity adverse events were likely drug-related due to the product's immunogenicity.[10] H_1-receptor antagonist, H_2-receptor antagonist, and/or antipyretics may be considered for premedication based on patient tolerability.[3]

FDA safety data includes 229 patients exposed to pegvaliase for 24 weeks, 209 patients exposed for 1 year, 137 patients exposed for 2 years, and 85 patients exposed for 3 years or longer.[3] As pegvaliase has the potential to be a life-long medication, extended long-term safety is still unknown.[3]

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

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Neuropsychiatric symptoms
2) Serious adverse events
3) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Reduction in blood phenylalanine concentration

Table 3. Pharmacology and Pharmacokinetic Properties.[3]

Parameter	
Mechanism of Action	Pegylated phenylalanine ammonia lyase enzyme that converts phenylalanine to ammonia and *trans*-cinnamic acid. Works by substituting for the deficient phenylalanine hydroxylase enzyme activity in patients with PKU and reduces blood phenylalanine concentrations.
Oral Bioavailability	N/A- administered subcutaneously
Distribution and Protein Binding	Mean apparent volume of distribution: 26.4 L in 20 mg once daily dose; 22.2 L in 40 mg once daily dose
Elimination	Mean apparent clearance at steady state: 0.39 L/hour in 20 mg once daily dose; 1.25 L/hour in 40 mg once daily dose Route of elimination has not been studied in humans
Half-Life	Mean half-life: 47 hours in 20 mg once daily dose; 60 hours in 40 mg once daily dose
Metabolism	Catabolic pathways; expected to be degraded into small peptides and amino acids

Abbreviations: L = liter; N/A = not applicable

Table 4. Comparative Evidence Table.

Ref./ Study Design	**Drug Regimens/ Duration**	**Patient Population**	**N**	**Efficacy Endpoints**	**ARR/NNT**	**Safety Outcomes**	**ARR/NNH**	**Risk of Bias/ Applicability**
1. Harding CO, et al[1] PRISM-2 Part 2: Randomized Discontinuation Trial	1. Pegvaliase 20 mg/d subq 2. Pegvaliase 40 mg/d subq 3. Placebo 20 mg/d subq	Demographics at PRISM-1 entry: • Age: 29.2 years • Female: 49.8% • White: 97.3% • Mean blood Phe: 1232.7 µmol/L	***PRISM-1*** ITT: 261 Attrition: 48 (18.4%)	Primary Endpoint: Change from start of RDT to week 8 in blood Phe concentration 1&2 (pooled). 26.5 µmol/L 95% CI -68.3 to 121.3 3. 949.8 µmol/L 95% CI 760.4 to 1139.1	NA	SAEs: 1&2 (pooled). 3.0% 3&4 (pooled). 3.4% AE causing study or study drug discontinuation: 1&2 (pooled). 0%	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: High. Patients who could not titrate to or maintain a maintenance dose of pegvaliase in PRISM-1 were not included in PRISM-2 Part 2. Additionally, patients who did not achieve a blood Phe reduction of ≥20% (from mean of 2 consecutive blood Phe assessments) from treatment-naïve baseline

DB, PC, 4 arm, discontinuation RCT PRISM-2 occurred immediately following PRISM-1 (Thomas, J et al[9])	4. Placebo 40 mg/d subq 8 weeks PRISM-2 occurred after PRISM-1 in which patients were titrated to a stable pegvaliase maintenance dosing regimen, so all patients had previously been on pegvaliase in Part 1 of PRISM-2.[9]	• Following Phe-restricted diet (>75% total protein intake from medical food): 15.7% Demographics at PRISM-2 Part 2 entry: • Age: 30.9 years • Female: 48.2% • White: 98.2% • Mean blood Phe: 520 µmol/L • Following Phe-restricted diet (>75% total protein intake from medical food): 5.8% Key Inclusion Criteria: • Age ≥18 years • Diagnosis of PKU • Received pegvaliase 20 mg/d or 40mg/d in Part 1 of PRISM-2 • If receiving neuropsychiatric medications, required stable dose • Willing & able to maintain stable protein intake • DC of sapropterin (≥14 d) & large neutral amino acids (≥2 d) prior to 1st pegvaliase dose (requirement of PRISM-1[9]) Key Exclusion Criteria (from PRISM-1[9] unless noted): • Use of injectable medication	***PRISM-2 Part 2*** mITT*: Total: 86 1. 29 2. 29 3. 14 4. 14 Attrition: Total: 14 (16.3%) 1&2 (pooled). 9 (15.5%) 3. 1 (7.1%) 4. 4 (28.6%)	4. 664.8 µmol/L 95% CI 465.5 to 864.1 P<0.0001 for pooled 1&2 vs. each placebo group 95% CI NR for comparative results Secondary Endpoints: Change from start of RDT to week 8 in ADHD RS-IV IA score for participants with baseline score >9: 1&2 (pooled). 3.1 3. -1.6 4. 0.28 *LS mean change:* *1&2 (pooled) vs. 3:* 4.7 95% CI -0.19 to 9.5; p=0.06 *1&2 (pooled) vs. 4:* 2.8 95% CI -2.0 to 7.5; p=0.24 Change from start of RDT to week 8 in ADHD RS-IV IA subscale score: 1&2 (pooled). 1.2 3. 0.74 4. -0.40 *LS mean change:* *1&2 (pooled) vs. 3:* 0.50 95% CI -2.1 to 3.1; p=0.70 *1&2 (pooled) vs. 4:* 1.6 95% CI -1.2 to 4.5; p=0.25 Change from start of RDT to week 8 in POMS score: 1&2 (pooled). 4.2 3. 7.2 4. 0.19 *LS mean change:* *1&2 (pooled) vs. 3:* -3.1 95% CI -18.6 to 12.5; p=0.70 *1&2 (pooled) vs. 4:* 4.0 95% CI -12.6 to 20.5; p=0.63	 NS NS NS NS NS NS	3&4 (pooled). 0% Hypersensitivity adverse events: 1&2 (pooled). 39.4% 3&4 (pooled). 13.8% Anaphylaxis: 1&2 (pooled). 0% 3&4 (pooled). 0% Generalized skin reaction >14 days: 1&2 (pooled). 7% 3&4 (pooled). 0% Injection site reaction: 1&2 (pooled). 16% 3&4 (pooled). 7% 95% CI & p-values NR for all outcomes		at the time of RDT entry were not included in PRISM-2 Part 2 mITT analysis. Randomized 2:1 to current dose of pegvaliase or placebo by IWRS. Stratified by blood Phe and ADHD RS-IV IA subscale score. Baseline characteristics balanced. Performance Bias: Low. Investigators, study staff, participants, and sponsor were blinded. Study drug self-injected subcutaneously. Matching placebo was used. Detection Bias: Low. Investigators and study staff blinded. Many secondary outcomes are subjective. Raters were trained at each site in administering neuropsychiatric assessment tools.[9] Attrition Bias: High. Attrition of 16.3% for PRISM-2 Part 2 eight week efficacy analysis, with high placebo attrition of 28.6%. Similar attrition in PRISM-1 (18.4%). Efficacy analysis based on mITT population of participants who had maintained pegvaliase dose from PRISM-2 Part 1 and had blood Phe reduction of ≥20% from treatment-naïve baseline at time of PRISM-2 Part 2 initiation. LOCF was used to impute data at monthly intervals for participants who terminated treatment early, which may lead to overestimation of efficacy results.[9] Reporting Bias: Unclear. Protocol not available. Study funded by BioMarin Pharmaceutical Inc. **Applicability**: Patient: All patients included in this trial had prior blood Phe reduction of ≥20% in PRISM-1. May not be applicable to patients who initially do not respond to pegvaliase or are initiating or titrating pegvaliase treatment. Included patients were limited to adults ≥18 years. Intervention: Subq medication able to be self-administered. Doses match FDA labeled dosing options of 20 or 40 mg/d. Patients were not allowed to be on concomitant sapropterin or large neutral amino acids.

		containing polyethylene glycol ≤3 months prior to screening • Patients pregnant, breastfeeding, or planning to become pregnant during study • PRISM-2 Part 2: Unable to titrate to or maintain maintenance dose of pegvaliase in PRISM-1		Change from start of RDT to week 8 in PKU-POMS score: 1&2 (pooled). 2.1 3. 5.2 4. 2.0 *LS mean change:* *1&2 (pooled) vs. 3:* -3.1 95% CI -10.3 to 4.1; p=0.40 *1&2 (pooled) vs. 4:* 0.08 95% CI -7.6 to 7.8; p=0.98	 NS NS			Comparator: Placebo appropriate for discontinuation trial. Outcomes: Blood Phe is a surrogate endpoint but commonly used in trials and accepted by the FDA as an appropriate PKU primary efficacy endpoint.[10] Guidelines recommend maintaining blood Phe levels in certain ranges lifelong due to neuropsychiatric complications which can occur with elevated levels. Evaluating blood Phe levels in a discontinuation trial does not measure maximum effect of the drug. Many secondary outcomes are subjective. Duration of 8 weeks was relatively short. Setting: Study centers in the United States (number unspecified for PRISM-2 Part 2 specifically; 29 in PRISM-2).[10]
Abbreviations [alphabetical order]: ADHD RS-IV IA = Attention Deficit Hyperactivity Disorder Rating Scale IV inattention subscale; AE = adverse event; ARR = absolute risk reduction; CI = confidence interval; D = days; DB = double-blind; DC = discontinuation; ITT = intention to treat; IWRS = interactive web response system; LS = least squares; MC = multicenter; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = not significant; PC = placebo controlled; PG = parallel-group; Phe = phenylalanine; PKU = phenylketonuria; POMS = Profile of Mood States score; PP = per protocol; RCT = randomized controlled trial; RDT = randomized discontinuation trial; SAE = serious adverse event; SUBQ = subcutaneously; U.S. = United States.								
*mITT population included patients who had maintained their pegvaliase dose of 20 mg/day or 40 mg/day in Part 1 of PRISM-2 and had a blood Phe reduction of ≥20% (from mean of 2 consecutive blood Phe assessments) from treatment-naïve baseline at the time of RDT entry. There were 39 patients identified in PRISM-2 Part 1 as being ineligible for PRISM-2 Part 2.[9] These patients entered into PRISM-2 Part 4 after PRISM-1 Part 1.[9]								

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Appendix 1: Prescribing Information Highlights

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

PALYNZIQ (pegvaliase-pqpz) injection, for subcutaneous use
Initial U.S. Approval: 2018

WARNING: RISK OF ANAPHYLAXIS
See full prescribing information for complete boxed warning.

- **Anaphylaxis has been reported after administration of Palynziq and may occur at any time during treatment. (5.1)**
- **Administer the initial dose of Palynziq under the supervision of a healthcare provider equipped to manage anaphylaxis, and closely observe patients for at least 60 minutes following injection. Prior to self-injection, confirm patient competency with self-administration, and patient's and observer's (if applicable) ability to recognize signs and symptoms of anaphylaxis and to administer auto-injectable epinephrine, if needed. (2.4)**
- **Prescribe auto-injectable epinephrine. Prior to first dose, instruct the patient and observer (if applicable) on its appropriate use. Instruct the patient to seek immediate medical care upon its use. Instruct patients to carry auto-injectable epinephrine with them at all times during Palynziq treatment. (2.4, 5.1)**
- **Palynziq is available only through a restricted program called the Palynziq REMS. (5.2)**

----------INDICATIONS AND USAGE----------
Palynziq is a phenylalanine-metabolizing enzyme indicated to reduce blood phenylalanine concentrations in adult patients with phenylketonuria who have uncontrolled blood phenylalanine concentrations greater than 600 micromol/L on existing management. (1)

----------DOSAGE AND ADMINISTRATION----------
Dosage (2.1)

- Obtain baseline blood phenylalanine concentration before initiating treatment.
- The recommended initial dosage is 2.5 mg subcutaneously once weekly for 4 weeks.
- Titrate the dosage in a step-wise manner over at least 5 weeks based on tolerability to achieve a dosage of 20 mg subcutaneously once daily. See full prescribing information for titration regimen.
- Assess patient tolerability, blood phenylalanine concentration, and dietary protein and phenylalanine intake throughout treatment.
- Consider increasing the dosage to a maximum of 40 mg subcutaneously once daily in patients who have been on 20 mg once daily continuously for at least 24 weeks and who have not achieved either a 20% reduction in blood phenylalanine concentration from pre-treatment baseline or a blood phenylalanine concentration less than or equal to 600 micromol/L.
- Discontinue Palynziq in patients who have not achieved at least a 20% reduction in blood phenylalanine concentration from pre-treatment baseline or a blood phenylalanine concentration less than or equal to 600 micromol/L after 16 weeks of continuous treatment with the maximum dosage of 40 mg once daily.
- Reduce the dosage and/or modify dietary protein and phenylalanine intake, as needed, to maintain blood phenylalanine concentrations within a clinically acceptable range and above 30 micromol/L.

Blood Phenylalanine Monitoring and Diet (2.2)

- Obtain blood phenylalanine concentrations every 4 weeks until a maintenance dosage is established.
- After a maintenance dosage is established, periodically monitor blood phenylalanine concentrations.
- Counsel patients to monitor dietary protein and phenylalanine intake, and adjust as directed by their healthcare provider.

Premedication (2.3, 5.1, 5.3)

- Consider premedication for hypersensitivity reactions.

Administration Instructions (2.4)

- Rotate injection sites. If more than one injection is needed for a single dose, the injection sites should be at least 2 inches away from each other.

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 2.5 mg/0.5 mL, 10 mg/0.5 mL, and 20 mg/mL in a single-dose prefilled syringe. (3)

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

----------WARNINGS AND PRECAUTIONS----------
Hypersensitivity Reactions, Other than Anaphylaxis: Management should be based on the severity of the reaction, recurrence, and clinical judgement, and may include dosage adjustment, temporary drug interruption, or treatment with antihistamines, antipyretics, and/or corticosteroids. (5.3)

----------ADVERSE REACTIONS----------
Most common adverse reactions (at least 20% in either treatment phase) are: injection site reactions, arthralgia, hypersensitivity reactions, headache, generalized skin reactions lasting at least 14 days, pruritus, nausea, abdominal pain, oropharyngeal pain, vomiting, cough, diarrhea, and fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact BioMarin Pharmaceutical Inc. at 1-866-906-6100, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
Effect of Palynziq on Other PEGylated Products: Monitor for hypersensitivity reactions, including anaphylaxis, with concomitant treatment. (7.1)

----------USE IN SPECIFIC POPULATIONS----------
Pregnancy: May cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 05/2018

PhenylketonuriaSapropterin

Goal(s):

- Promote safe and cost effective therapy for the treatment of phenylketonuria.

Length of Authorization:

- Initial: 1 to 92 months;
- Renewal: 16 weeks to 1 year

Requires PA:

- Sapropterin and pegvaliase (pharmacy and physician administered claims)

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated and is the requested treatment funded by the OHP for that conditionIs the diagnosis funded by OHP? Note: Treatments which appear on an unfunded line of the prioritized list are not funded by the OHP	**Yes:** Go to #2	**No:** Pass to RPh. Deny; not funded by OHP
2. Is the request for renewal of therapy previously approved by the FFS system?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is the drug prescribed by or in consultation with a specialist in metabolic disorders?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the request for sapropterin?	**Yes:** Go to #5	**No:** Go to #8

Approval Criteria		
~~4.~~5. Is the diagnosis tetrahydrobiopterin- (BH4-) responsive phenylketonuria?	**Yes:** Go to #~~6~~5	**No:** Pass to RPh. Deny; medical appropriateness
~~5.~~6. Is the patient currently compliant with a Phe-restricted diet and unable to achieve target blood phenylalanine level?	**Yes:** Go to #~~7~~6	**No:** Pass to RPh. Deny and recommend Phe-restricted diet.
~~6.~~7. Is the patient's baseline blood phenylalanine level provided in the request and above the target range (see Clinical Notes)?	**Yes:** Approve for 2 months if initial dose is 5-10 mg/kg/day (to allow for titration to 20 mg/kg/day). Approve for 1 month if initial dose is 20 mg/kg/day (adults and children).	**No:** Request information from provider.
8. Is the request for pegvaliase?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Is the patient 18 years of age or older with a diagnosis of phenylketonuria?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness
10. Is the patient's blood phenylalanine concentration documented in the request and greater than 600 µmol/L on existing management (such as dietary phenylalanine restriction or sapropterin)?	**Yes:** Approve for 9 months based on FDA-approved induction, titration, and maintenance dosing*	**No:** Pass to RPh. Deny; medical appropriateness. If not documented, request information from provider.

Renewal Criteria		
1. Is the request for sapropterin?	**Yes:** Go to #2	**No:** Go to #4

Renewal Criteria		
~~1.~~2. Did the patient meet the target phenylalanine level set by the specialist (see Clinical Notes)?	**Yes:** Go to #3	**No:** Pass to RPh. Deny for lack of treatment response.
~~2.~~3. Is the patient remaining compliant with the Phe-restricted diet?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny and recommend Phe-restricted diet.
4. Is the request for pegvaliase?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Has there been a reduction from baseline phenylalanine concentration of 20% or greater?	**Yes:** Approve for 12 months	**No:** Go to #6
6. Has there been a reduction in blood phenylalanine concentration to less than or equal to 600 µmol/L?	**Yes:** Approve for 12 months	**No:** Go to #7
7. Is the request for a first renewal of pegvaliase therapy and the patient had been on pegvaliase 20 mg daily for at least 24 weeks?	**Yes:** Approve for 16 weeks for trial of maximum dose of 40 mg once daily. Continued approval at this dose requires documentation of improvement (>20% reduction from baseline or less than 600 µmol/L in phenylalanine concentration).	**No:** Pass to RPh. Deny for lack of treatment response.

Clinical Notes:

Target blood phenylalanine levels in the range of 120-360 µmol/L for patients in all age ranges.[1]

In addition to the recommended Phe concentrations, a 30% or more reduction in blood Phe is often considered a clinically significant change from baseline and should occur after the initial trial.[2] If not, the patient is a non-responder and will not benefit from sapropterin therapy.

Sapropterin d~~D~~oses above 20 mg/kg/day have not been studied in clinical trials.

***Pegvaliase FDA-Recommended Dosage and Administration:**

Treatment	Pegvaliase Dosage	Duration*
Induction	2.5 mg once weekly	4 weeks
Titration	2.5 mg twice weekly	1 week
	10 mg once weekly	1 week
	10 mg twice weekly	1 week
	10 mg four times per week	1 week
	10 mg once daily	1 week
Maintenance	20 mg once daily	24 weeks
Maximum**	40 mg once daily	16 weeks***

*Additional time may be required prior to each dosage escalation based on patient tolerability.
**Individualize treatment to the lowest effective and tolerated dosage. Consider increasing to a maximum of 40 mg once daily in patients who have not achieved a response (>20% reduction in blood phenylalanine concentration from pre-treatment baseline or a blood phenylalanine concentration <600 µmol/L) with 20 mg once daily continuous treatment for at least 24 weeks.
***Discontinue pegvaliase treatment in patients who have not achieved a response (>20% reduction in blood phenylalanine concentration from pre-treatment baseline or a blood phenylalanine concentration <600 µmol/L) after 16 weeks of continuous treatment with the maximum dosage of 40 mg once daily.

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P&T Review: *9/18 (JP); 5/16; 11/13; 9/13; 7/13*
Implementation: *TBD; 8/16; 1/1/14*

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Drug Class Update: Hepatitis C Direct-Acting Antivirals

Date of Review: September 2018

Date of Last Review: September 2017
End Date of Literature Search: 08/2018

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

Purpose for Class Update:
To evaluate new comparative evidence of the benefits and harms of direct-acting antivirals (DAAs) for the treatment of chronic hepatitis C (CHC). Additionally, evidence for effectiveness of DAAs in people who inject drugs (PWIDs) will be reviewed.

Research Questions:
1. Is there new comparative evidence for differences in efficacy/effectiveness or harms between available DAAs for the treatment of CHC?
2. Are there specific subpopulations based on severity of disease, extrahepatic manifestations, comorbidities, or level of fibrosis that may benefit from one particular DAA over another DAA or benefit from immediate treatment?
3. Is there new evidence to support an optimal time to initiate treatment for CHC based on improved effectiveness or less harms?
4. Is there new evidence that achieving a sustained viral response (SVR) with DAAs results in long term improvement in clinically meaningful outcomes, including mortality, cirrhosis, liver transplantation, serious extrahepatic manifestations and hepatocellular carcinoma (HCC)?
5. Is there data that DAAs are effective and safe for the treatment of CHC in PWIDs?

Conclusions:
- There is insufficient evidence to evaluate whether eliminating hepatitis C virus (HCV) with the DAAs improves death or clinical manifestations of HCV associated cryoglobulinemia.[1]
- There is insufficient evidence that treatment with DAAs are effective in the treatment of acute HCV to reduce progression to CHC or cirrhosis, decrease mortality, or improve quality of life.[2]
- There are no data from randomized controlled trials evaluating the impact of treatment programs including needle syringe programs and/or opioid substitution therapy with methadone or buprenorphine in reducing the transmission of HCV in PWID.[3]
- There are no data suggesting a minimum length of abstinence to improve outcomes associated with treatment of CHC or that patients are less likely to achieve SVR with similar adherence.

Direct Acting Antiviral Abbreviations: **DCV/SOF** (Daclatasvir + sofosbuvir): Daklinza® + Sovaldi®; **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **G/P** (glecaprevir/pibrentasvir): Mavyret®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; **OMB/PTV-R + DAS** (ombitasvir, paritaprevir and ritonavir with dasabuvir): Viekira Pak®/Viekira XR®; **OMB/PTV-R** (ombitasvir, paritaprevir and ritonavir): Technivie®; **SOF/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®; **SOF/VEL/VOX** (sofosbuvir/velpatasvir/voxilaprevir): Vosevi®

- There is low quality evidence based on observational data only with moderate to high risk of bias due to potential confounding that opioid substitution therapy alone (relative risk [RR] 0.50; 95% CI 0.40 to 0.63) or in combination with needle syringe programs (RR 0.26; 95% CI 0.07 to 0.89) reduces HCV incidence among PWID and that needle syringe programs alone do not reduce HCV incidence among PWID (RR 0.79; 95% CI 0.39 to 1.61).[3]
- There is low quality evidence SVR rates at 12 weeks (SVR12) with SOF/VEL with or without opioid substitution therapy or EBR/GZR with opioid substitution therapy in PWID are greater than or equal to 90% and SVR24 rates with EBR/GZR in patients receiving opioid substitution therapy are approximately 85%.

Recommendations:
- Approve updated prior authorization (PA) criteria (**Appendix 4**). Remove the treatment requirements for those with substance use disorder, alcohol abuse and illicit injectable drug use and incorporate the necessary additional support into case management programs.
- Allow treatment of HCV in PWID while supporting harm reduction treatment programs, including opioid substitution treatment programs, when available.

Summary of Prior Reviews and Current Policy
- There is low quality evidence that the DAA regimens are effective in achieving a SVR rate of greater than or equal to 90%. SVR rates differ between patients based on disease severity, genotype, and baseline NS5a resistant amino acid variants (RAVs). Relapse may be reduced with baseline NS5A polymorphism screening.
- The regimens that have been studied in patients with cirrhosis include mostly Child-Pugh A and B. There are very limited data in Child-Pugh C.
- From the only comparative data available, there is low quality evidence that 12 weeks SOF/VEL may be modestly superior to 12 weeks SOF + RBV in patients with GT2 (SVR 99% vs. 95%, respectively; absolute difference 5.2%; 95% CI, 0.2-10.3%; p=0.02). Treatment with 12 weeks of SOF/VEL may also be superior to 24 weeks of SOF + RBV in patients with GT3 (SVR 95% vs. 80%; respectively; absolute difference 14.8%; 95% CI 9.6-20%; p<0.001). There are no other alternative treatment regimens approved for GT2, and there is insufficient comparative data for other treatments available for GT3 (LDV/SOF + RBV or DCV/SOF).
- There are still several limitations in the current evidence for the treatment of CHC:
    - There is still insufficient evidence for the optimal treatment of patients who have had a virologic failure to a previous NS5A or NS5B inhibitor. Risk of DAA resistance is a major concern in this population.
    - There is still a lack of head-to-head trials for most DAA regimens. In some populations, data on DAAs are limited to open-label, uncontrolled, or historically controlled trials.
    - Trials often exclude patients with chronic hepatitis B virus (HBV), HIV, cancer, HCC, decompensated cirrhosis, severe psychiatric, cardiac, pulmonary, or renal comorbidities, and severe alcohol or substance abuse. When decompensated cirrhosis is included, there are very little data in patients with Child-Pugh class C.
    - There is no direct evidence that treatment with antiviral therapy for CHC leads to improved long-term clinical outcomes in incidence of HCC, liver transplantation, or mortality.
- The Oregon Drug Use Review/Pharmacy & Therapeutics (P&T) Committee initially prioritized treatment for the fee-for-service population to patients in greatest need of treatment. Limited real-world experience and data, consideration for the number of patients waiting for treatment, limited provider expertise, and the limited number of alternative treatment options in cases of treatment resistance and patient comorbidities all played a role in prioritizing treatment. As more treatment options become available, real world experience increases, and the community standard evolves, the P&T Committee has

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expanded treatment in a step-wise fashion to patients with less severe disease. Current drug policies in place approve treatment for patients with fibrosis Metavir stage 2 or greater, or patients with extrahepatic manifestations or HIV at any stage of fibrosis, and patients in the setting of solid organ transplant.

Background:

Chronic hepatitis C (CHC) infection is the leading cause of complications from chronic liver disease, including cirrhosis, liver failure, and hepatocellular carcinoma (HCC). It is also the leading indication for liver transplantation in the Western world.[4] The global prevalence is 1.6%, and in the United States (U.S.) approximately 50% of affected individuals remain unaware of their diagnosis.[5] The goal of treatment for CHC is to reduce the occurrence of end-stage liver disease and its related complications. However, results from clinical trials designed to evaluate long-term health outcomes or health related quality of life are not available. In addition, only about 10-20% of people with CHC develop cirrhosis (8-16% of all people infected with HCV), and the time to progress to cirrhosis varies at an average of 40 years.[5] Approximately 20% of individuals infected with HCV will clear the virus. HCV is divided into seven major genotypes (GT) with variable geographical distribution and prevalence. In the U.S., GT1 infection is found in about 75% of patients with CHC; GT2 and GT3 represent about 20% of CHC patients.[4] The most common subgenotypes of GT1 are 1a and 1b. Cure rates for GT 1a and 1b infection may differ depending on the treatment regimen. Data suggests that fibrosis progression occurs most rapidly in patients with GT3; DAA regimens have also been less effective in patients with this genotype.[6]

The SVR rate is defined as the proportion of patients who experience a decline in HCV-RNA to undetectable levels following completion of antiviral treatment, as measured by a sensitive polymerase chain reaction assay. It is the standard marker of successful treatment in clinical trials. There is some evidence based on only observational data of an association of SVR and reductions in mortality, liver failure, and cancer.[4] However, the results of these observational studies should be interpreted with great caution. SVR is still a non-validated, surrogate outcome, and it is not clear that SVR is a 'cure' for HCV. Many of the observational studies compared two groups that were both treated making it difficult to attribute different outcomes to treatment.[5] SVR has previously been shown as an invalid surrogate for clinical outcomes for the efficacy of interferons.[5] Trials have historically used SVR at week 24 of follow-up (SVR24) as a primary endpoint. More recent studies use SVR rate at 12 weeks (SVR12) as the primary endpoint based on evidence that the majority of patients with SVR12 maintain SVR at 24 weeks.[7]

The two major predictors of SVR are viral genotype and pre-treatment viral load.[8] Other factors associated with an increased likelihood of SVR include female sex, age less than 40 years, non-Black race, lower body weight, absence of insulin resistance, and absence of bridging fibrosis or cirrhosis on liver biopsy. Studies that include patients with decompensated cirrhosis, renal failure or other comorbidities, and minority racial or ethnic groups are lacking though these patients remain the most difficult to successfully treat.[9]

Patients at greatest risk for progression to cirrhosis have detectable HCV-RNA and liver histology demonstrating fibrosis (METAVIR stage 2 or higher). Patients with compensated cirrhosis are at risk of progressing to decompensation, developing hepatocellular carcinoma, and are at higher risk for death. Urgency to treat patients with CHC is higher when risk of decompensated cirrhosis or death from liver-related diseases is higher; treatment urgency is also higher in liver transplant recipients with CHC in order to prolong graft survival. Disease progression varies greatly among patients with compensated liver disease, and the number needed to treat to prevent adverse long-term outcomes is dependent on several factors. The newer DAAs will be most beneficial in patients at highest risk for cirrhosis-related events.[10] However, treatment of CHC with DAAs at earlier stages of fibrosis incur substantial upfront costs but can be cost-effective long-

term if adverse events are avoided from cure.[11] Patients with decompensated liver disease are a challenging population to treat because of symptomatic complications related to cirrhosis (i.e., jaundice, ascites, variceal hemorrhage, or hepatic encephalopathy). Clinical trials define decompensated cirrhosis as Child-Turcotte-Pugh (CTP) class B or C cirrhosis; the majority of decompensated cirrhosis patients included in trials have CTP class B cirrhosis. Those with stage 3 to 4 disease develop end stage liver disease at a rate of 1 to 2% per year after achieving SVR.[5]

Virologic failure is defined as confirmed HCV RNA level at or above the lower limit of quantification (LLOQ) during treatment after previously being below the LLOQ; relapse is defined as confirmed HCV RNA level at or above the LLOQ after treatment after previously achieving an SVR.[12] Virologic failure is typically associated with the emergence of resistance-associated variants (RAVs) that can cause cross resistance to other DAAs in the same class.[13] Baseline RAVs exist in a minority of patients and are found in most patients who fail to achieve SVR with DAA treatment. Sofosbuvir (SOF), an NS5B inhibitor, appears to have the highest genetic barrier to resistance.[13] Genetic polymorphisms that reduce drug susceptibility have been reported for the NS5A and NS3/4A (protease inhibitor) drug classes. The presence of baseline NS5A RAVs has been reported in the range from 1% to 23% and can significantly reduce SVR12 rates in patients with GT3 treated with daclatasvir (DCV) plus SOF compared to patients without the NS5A RAV (SVR rates of 54% vs. 92%, respectively).[14] Another review of 35 clinical trials in patients with HCV GT1 found that pretreatment NS5A RAVs were detected in 13% of GT 1a and 18% with GT 1b and had an impact on SVR in some patients, particularly treatment-experienced patients with GT 1a HCV.[15]

Therapies to treat CHC have advanced significantly over the past several years. Prior to 2011, the combination of pegylated interferon (PEG-IFN) and ribavirin (RBV) was the standard of care and approximately only 55-60% of patients achieved a SVR with this regimen. In 2011, the FDA approved the first generation DAAs boceprevir and telaprevir.[16] The DAAs target specific proteins of the virus, causing disruption of viral replication. There are currently four classes of DAAs, defined by their mechanism of action and therapeutic target (NS3/4A inhibitors, protease inhibitors [PIs], NS5B inhibitors and NS5A inhibitors). Due to adverse events, high rates of resistance and long duration of treatments, telaprevir was removed from the market and boceprevir is no longer a recommended therapy. Since then, a variety of second generation DAAs have been approved by the FDA resulting in many interferon-free options, fewer adverse events, and SVR12 rates that exceed 90% (**Table 1**). However, newer DAAs are associated with substantial cost and unknown effects on long-term clinical outcomes. A significant challenge is to identify patients who will most benefit from treatment since only 5-20% of CHC patients will develop cirrhosis over 20 years.[17] Additionally, the lack of head-to-head trials, and the use of single-arm cohort studies make it difficult to compare the relative efficacy of the different DAA regimens available. Studies do not measure long-term morbidity or mortality.

Table 1. Direct-acting Antiviral Regimens for Chronic Hepatitis C.*

Drug Brand Name	Generic name	Indications	Decompensated Cirrhosis	Mechanism of Action	Duration
Daklinza® and Solvaldi®	Daclatasvir + sofosbuvir	CHC GT 1 or GT 3	GT 1, 3 with RBV	NS5A inhibitor with NS5B inhibitor	12 weeks
Epclusa®	Sofosbuvir/velpatasvir	CHC GT 1-6	GT 1-6, with RBV	NS5B inhibitor/NS5A inhibitor	12 weeks
Harvoni®	Ledipasvir/sofosbuvir	CHC GT 1; GT 4; GT 5; GT 6	GT 1 with RBV	NS5A inhibitor/ NS5B inhibitor	8, 12, or 24 weeks

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Mavyret®	Glecaprevir/pibrentasvir	CHC GT 1-6 without cirrhosis or compensated cirrhosis and GT 1 previously treated with a NS5A inhibitor or an NS3/4a protease inhibitor	Contraindicated	NS3/4A protease inhibitor/NS5A inhibitor	8-16 weeks
Olysio®	Simeprevir	CHC GT 1 in combination with sofosbuvir	Not approved	NS3/4A protease inhibitor	12 -24 weeks
Sovaldi®	Sofosbuvir	CHC GT 1; GT 2; GT 3; GT 4 Used in combination with other antivirals	Not approved	Nucleotide analog NS5B polymerase inhibitor	12 weeks
Vosevi®	sofosbuvir/velpatasvir/voxilaprevir	CHC GT 1-6 TE with NS5A inhibitor; GT 1a or 3 TE with sofosbuvir and without an NS5A inhibitor	Contraindicated	NS5B inhibitor/NS5A inhibitor/NS3 protease inhibitor	12 weeks
Zepatier®	Elbasvir / grazoprevir	CHC GT 1; GT 4	Contraindicated	NS3/4A protease inhibitor/ NS5A inhibitor	12 or 16 weeks
Abbreviations: CHC = chronic hepatitis C; GT = genotype, RBV: ribavirin; TE: treatment-experienced *Viekira Pak/Viekira XR and Technivie have been discontinued and will no longer be available after January 2019					

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. If these trials are not available, trials using a historical SVR will be considered. 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), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Institute for Clinical and Economic Review (ICER), 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. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated evidence-based clinical practice guidelines.

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.

For use of the DAAs in PWID, observational trials will be considered.

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New Systematic Reviews:
After review, 9 systematic reviews were excluded due to poor quality, wrong study design of included trials (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical).[18-26]

A systematic review from the Cochrane Collaboration evaluated the benefits and harms of treatment options for HCV-associated cryoglobulinemia with active manifestations of vasculitis.[1] One such therapeutic approach is eliminating HCV infection. The primary outcomes were death and decreasing clinical manifestations (i.e. kidney disease, skin vasculitis, musculoskeletal symptoms, liver involvement, interstitial lung involvement, and widespread vasculitis). Ten studies met inclusion criteria and were identified for review, all of which evaluated immunosuppressive medications (rituximab), interferon therapy or extracorpeal therapies. Although elimination of HCV with DAAs is the current mainstay of treatment, there were no published or ongoing studies evaluating the DAAs in patients with HCV-associated cryoglobulinemia.

A second systematic review from the Cochrane Collaboration assessed the comparative benefits and harms of pharmacological interventions in the treatment of acute HCV.[2] Interferon and DAAs have been used to attempt to eradicate acute HCV and prevention progression to CHC. The primary outcomes of interest were mortality, adverse events, and quality of life. Ten trials were identified and included in the review (n=488). All of the trials compared interferon or pegylated interferon to other interventions. Overall, there was very low-quality evidence that interferon-alfa may decrease the incidence of CHC as measured by SVR. However, there was no evidence on quality of life, reduction in cirrhosis, decompensated liver disease and liver transplantation. These results are also not applicable today since DAAs have become the standard of care. None of the trials compared DAAs to any other interventions.

The efficacy and safety of 12 weeks of LDV/SOF versus LDV/SOF + RBV in patients with CHC GT 1 with cirrhosis or who have failed prior therapy was evaluated in a recent systematic review of randomized controlled trials. [27] Current guidelines recommend LDV/SOF + RBV or extending the duration of LDV/SOF to 24 weeks in patients with cirrhosis or with failure of previous treatment. However, this is based on expert opinion only. The authors of this review had no conflicts of interest to disclose. Study quality was assessed independently by two authors using the Cochrane Collaboration risk of bias tool. Only four trials met inclusion criteria and were included in the review. The proportion of patients with cirrhosis ranged from 20% to 100% in the included studies, and all studies excluded those with HIV coinfection, chronic hepatitis B, and decompensated cirrhosis. All of the trials had a high risk of bias associated with non-blinded methods and for being funded and conducted by Gilead Sciences, the manufacturer of LDV/SOF. Among cirrhotic patients who failed previous therapy, the pooled relative risk (RR) of not achieving SVR12 after completing 12 weeks of LDV/SOF compared to 12 weeks of LDV/SOF + RBV was 1.21 (95% CI 0.42 to 3.48). However, with the wide confidence interval and pooled effect size over a 20% increase in the risk of failure to achieve SVR, the authors concluded the study could not confirm that 12 weeks of LDV/SOF is noninferior to LDV/SOF + RBV. Furthermore, adverse effects were significantly less common in those not receiving RBV (RR 0.11; 95% CI 0.04 to 0.29).

New Guidelines:
After review, two guidelines were excluded due to poor quality.[28,29]

Guidelines from the Veterans Affairs (VA) National Hepatitis C Resource Center were updated in October 2017 to include all available agents and update options for re-treatment (**Table 2**).[14] In addition to updated treatment regimens, the guidelines recommend RAS testing only be performed if results would guide re-

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treatment options. Additional recommendations are included before for easy comparison to other treatment guidelines. The guidelines continue to recommend that HIV/HCV-coinfected patients receive the same HCV antiviral regimens as HCV monoinfected patients unless LDV/SOF is being considered, in which case a 12-week regimen should be used (instead of an 8-week regimen).

Additional Guidelines for Clinical Context:

The World Health Organization (WHO) updated their guidelines for the screening care and treatment of persons with CHC in April 2016,[30] and the Guidelines from the American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) updated their recommendations for testing, managing, and treating CHC in September 2017 to include the latest DAA regimens (SOF/VEL/VOX and G/P) and in May 2018.[6] The AASLD/IDSA guidelines are routinely updated to reflect rapidly changing evidence with the DAAs.[6] The AASLD/IDSA guideline has many limitations with poor methodological quality. The panel lacks non-specialist members, and there is no assessment of risk of bias for individual studies. In addition, the authors and sponsors of the guideline have multiple conflicts of interest. The guidelines are provided for clinical context, but decisions based on these guidelines should be made with caution.

The AASLD/IDSA guidelines were updated in May 2018 with the following changes:

1. Treatment of CHC in pregnancy:
    a. Universal screening of all pregnant women, ideally at the initiation of prenatal care.
    b. Treatment during pregnancy is not recommended due to the lack of safety and efficacy data with DAAs.
    c. For women of reproductive age with CHC, antiviral therapy is recommended before pregnancy is considered.
2. Management of CHC in PWID:
    a. Annual HCV testing is recommended
    b. Substance use disorder treatment programs and needle/syringe exchange programs should offer routine, opt-out HCV-antibody testing with linkage to care for those infected
    c. PWID should be offered to harm reduction services when available (needle/syringe service programs and substance use disorder treatment programs)
    d. Active or recent drug use or a concern for reinfection is not a contraindication to HCV treatment
3. Management of CHC in men who have sex with men (MSM):
    a. Annual HCV testing is recommended for sexually active HIV-infected MSM.
    b. HCV testing at HIV pre-exposure prophylaxis (PrEP) initiation and at least annually is recommended at least annually thereafter in HIV-uninfected MSM.
    c. All MSM should be counseled about the risk of sexual HCV transmission with high risk sexual and drug practices
    d. Antiviral treatment should be coupled with ongoing counseling about the risk of HCV reinfection, and education about methods to reduce HCV reinfection risk after cure
4. Management of CHC in correctional settings
    a. Jails should implement opt-out HCV testing

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b. Chronically infected individuals whose jail sentence is sufficiently long to complete a recommended course of antiviral therapy should receive treatment while incarcerated
c. Jails and prisons should facilitate continuation of HCV therapy for individuals on treatment at the time of incarceration

The following recommendations are included in these guidelines:

When to Treat:
AASLD/IDSA: Treatment for all patients regardless of disease severity is recommended, except those with short life expectancy that cannot be remediated by treatment or transplantation.[6] Little evidence exists to support initiation of treatment in patients with limited life expectancy. Prior to treatment, the guideline continues to emphasize the need to assess the patient's understanding of treatment goals and provision of education on adherence and follow-up.

WHO: HCV treatment should be considered for all persons with CHC, including persons who inject drugs. Persons with cirrhosis should be prioritized for treatment because they are at increased risk of HCC and death due to liver failure.

VA: All patients with CHC who do not have medical contraindications are potential candidates for treatment. Patients with advanced liver disease are likely to derive the greatest benefit from treatment.[14] The urgency of treatment should be based on the risk of developing decompensated cirrhosis or dying from liver or liver-related disease, and prolonging graft survival in transplant recipients. In particular, patients with cirrhosis or advanced fibrosis, selected patients with HCC awaiting liver transplant, post-transplant recipients, patients with serious extra-hepatic manifestations of HCV, and women of childbearing potential who desire to conceive a child in the next 12 months should be considered for antiviral treatment in the near term. Patients with mild liver disease (METAVIR F0-2) have less urgency for treatment in the short-term but should be informed of current treatments and the potential to cure HCV. Patients with mild liver disease (METAVIR F0-2) and no extra-hepatic manifestations can be treated in the near term if the patient desires treatment and is otherwise a candidate for HCV treatment.

Who Should Treat:
With all-oral shorter course regimens, treatment may be increasingly available outside of specialty clinics. Guidelines recommend that therapy should be managed by medical specialists with experience in the treatment of CHC infection and the physician prescribing should have knowledge of monitoring and ensuring patient adherence with therapy. The VA guideline states treatment can be provided by non-specialists trained in the management of CHC and who have access to specialists for support (Expert Opinion).[14] However, patients with decompensated cirrhosis should be seen by a specialist with experience in the management of advanced disease.

Fast Progressing:
Progression of fibrosis from stage 0 (no fibrosis) to stage 4 (cirrhosis) is variable but takes place at approximately 0.10-0.15 fibrosis units per decade.[31] The AASLD/IDSA guidelines includes the following patient populations to be at greater risk for rapidly progressive fibrosis and cirrhosis:

- HIV coinfection
- HBV coinfection and other coexistent liver disease (nonalcoholic steatohepatitis [NASH]): Several observational studies have found coinfected patients have more severe liver disease than those with monoinfection.[32] However, there are no longitudinal studies to evaluate the rate of fibrosis progression

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in coinfected subjects, and most data comes from studies with a small sample size and retrospective design.[33] Additional studies with similar limitations have conflicting results. There are no published studies evaluating DAA regimens in patients with HBV/HCV coinfection.

Extrahepatic Manifestations:
The literature has linked HCV to a number of extrahepatic symptoms involving the skin, musculoskeletal, renal, cardiovascular and nervous systems.[34] There are no RCTs evaluating the effects of DAA-based regimens on progression of extrahepatic complications, and most of the literature consists of observational studies with risk for selection bias which demonstrate an association between progression and treatment. The quality of the evidence for these associations is extremely variable, and it is difficult to make definitive conclusions regarding the effect of DAAs on progression of extrahepatic manifestations. The following extrahepatic manifestations have been identified:

- Cryoglobulinemia and lymphoproliferative disorder
- Dermatologic manifestations: leukocytoclastic vasculitis, porphyria cutanea tarda, lichen planus
- Insulin Resistance and Type 2 Diabetes: There is growing observational evidence that HCV increases the risk of T2DM through induction of insulin resistance and that T2DM can accelerate the course of CHC.[35]
- Lymphomas (B-cell non-Hodgkin lymphoma)

Alcohol and Drug Abuse Recommendations:
AASLD/IDSA: Abstinence from alcohol and, when appropriate, interventions to facilitate cessation of alcohol consumption should be advised for all persons with HCV infection. Persons identified as abusing alcohol and having alcohol dependence require treatment and consideration for referral to an addiction specialist. For individuals with acute HCV infection who have a history of recent injection drug use, referral to an addiction medicine specialist is recommended when appropriate.[6]

WHO: An alcohol intake assessment is recommended for all persons with HCV infection followed by the offer of a behavioral alcohol reduction intervention for persons with moderate-to-high alcohol intake. Persons who inject drugs should be assessed for antiviral treatment. Persons who inject drugs are at increased risk of HCV-related disease and transmission, as well as for all-cause morbidity and mortality, and therefore require specialized care and should be considered as a priority for HCV treatment.[30]

VA: Ongoing substance use involving alcohol, illicit drugs, and marijuana, or participation in an opioid replacement program, should not be an automatic exclusion criterion for HCV treatment. However, in some patients, substance use or alcohol use disorders may need to be addressed prior to initiation of HCV treatment because of the risk of non-adherence and reinfection.

Decisions regarding HCV treatment of patients with substance use disorders or severe mental health conditions should be made by an experienced provider who can assess the likelihood of adherence with medical recommendations, clinic visits, and medications. All patients should be evaluated for current alcohol and other substance use, with validated screening instruments such as AUDIT-C (www.hepatitis.va.gov/provider/tools/audit-c.asp).[14] Patients with a history of substance or alcohol use disorders should be considered for HCV antiviral therapy on a case-by-case basis. There are no published data supporting a minimum length of abstinence as an inclusion criterion for HCV antiviral treatment, while multiple studies show successful treatment of patients who have short durations

of abstinence or infrequent use of alcohol. Thus, automatic disqualification of patients as treatment candidates based on length of abstinence is unwarranted and strongly discouraged. The presence of current heavy alcohol use (>14 drinks per week for men or >7 drinks per week for women), binge alcohol use (>4 drinks per occasion at least once a month), or active injection drug use warrants referral to an addiction specialist before treatment initiation. Patients with active substance or alcohol use disorders may be considered for therapy on a case-by-case basis, and care should be coordinated with substance use treatment specialists.[14]

Testing for Liver Cirrhosis:
AASLD/IDSA: The use of biopsy, imaging, and/or noninvasive markers appropriate to evaluate advanced fibrosis should be considered in HCV patients planning on treatment (Class I, Level A).[6] Guidelines also recommend that a biopsy should be considered for any patient with discordant results between 2 modalities that would affect clinical decision making. If direct biomarkers or elastography are not available, the AST-to-platelet ratio index (APRI) or FIB-4 index score can help, although neither test is sensitive enough to rule out significant fibrosis.

WHO: In resource-limited settings, it is suggested that the APRI or FIB-4 test be used for the assessment of hepatic fibrosis rather than other noninvasive tests that require more resources such as elastography or FibroTest (Conditional recommendation, low quality of evidence). FibroScan, which is more accurate than APRI and FIB-4, may be preferable in settings where the equipment is available and the cost of the test is not a barrier to testing.[30]

VA: Testing recommendations include clinical findings (low platelet count), abdominal imaging for features of portal hypertension, liver fibrosis imaging (FibroScan and Acoustic Radiation force impulse [ARFI]), serum markers of fibrosis (APRI, FIB-4, FibroSure, FibroTest), and liver biopsy as options. Liver biopsy should be reserved for situations in which the risks and limitations of the procedure are outweighed by the benefits of obtaining information via this technique.[14]

Decompensated Cirrhosis:
All guidelines recommend patients with decompensated cirrhosis be considered for treatment on a case by case basis and should involve an experienced specialist who is able to manage complications.

Recommendations for performing pre-treatment resistant testing:
The VA guidelines recommend that NS5A resistance-associated variants (RAV) testing should be performed at baseline prior to initial treatment for GT 1a-infected patients who are being treated with EBR/GZR and for GT3 patients being treated with SOF/VEL to determine if RBV is needed.[14]

Retreatment:
The AASLD/IDSA guidelines have retreatment recommendations for those who have failed treatment with PEG/RBV or PEG/RBV + a NS3 PI (telaprevir, boceprevir, or simeprevir) that are similar to initial treatment recommendations for GT1 (Table 2). For those who have failed sofosbuvir plus RBV, LDV/SOF is the recommended therapy for GT1 based on limited data. For NS5A treatment-experienced patients, the guidelines recommend the newer agents, SOF/VEL/VOX or G/P with a higher strength of recommendation for SOF/VEL/VOX.[6]

Recommended Treatment Options:

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Treatment options based on genotype and treatment history are included in the following table:

Table 2: Guideline Recommended Treatment Options

GT	Treatment History	Cirrhosis Status	Veterans Affairs Guidelines[14]	AASLD/IDSA Guidelines[6]	WHO Guidelines[30]
1	***Naïve or Experienced (PEG-INF/RBV only)***	***Non-cirrhotic***	EBR/GZR x 12 weeks ** LDV/SOF x 8-12 weeks (8 weeks if HCV RNA <6 million IU/ml and HCV-monoinfected) G/P x 8 weeks SOF/VEL x 12 weeks	EBR/GZR x 12 weeks** LDV/SOF x 8-12 weeks (8 weeks if RNA <6 million IU/ml, non-black and HCV-monoinfected) G/P x 8 weeks SOF/VEL x 12 weeks	DCV/SOF x 12 weeks LDV/SOF x 8-12 weeks
1		***Cirrhotic***	LDV/SOF x 12 weeks EBR/GZR x 12 weeks G/P x 12 weeks SOF/VEL x 12 weeks	LDV/SOF x 12 weeks EBR/GZR x 12 weeks** G/P x 12 weeks SOF/VEL x 12 weeks	DCV/SOF +/- RBV x 12 weeks LDV/SOF +/- RBV x 12 weeks
1		***Decompensated Cirrhosis***	LDV/SOF + RBV x 12 weeks SOF/VEL + RBV x 12 weeks	LDV/SOF + RBV x 12 weeks SOF/VEL + RBV x 12 weeks DCV/SOF + RBV x 12 weeks	DCV/SOF x 12 weeks
1	***Experienced (prior sofosbuvir)***	***Non-cirrhotic or compensated cirrhosis***	G/P x 8-12 weeks SOF/VEL x 12 weeks	G/P x 12 weeks SOF/VOL x 12 weeks (GT 1 b) SOF/VEL/VOX x 12 weeks (GT 1a)	N/A
1	***Experienced (Prior NS3A/4A inhibitor)***	***Non-cirrhotic or compensated cirrhosis***	G/P x 8-12 weeks (8 weeks if non-cirrhotic) SOF/VEL x 12 weeks LDV/SOF +/- RBV x 12 weeks	G/P x 12 weeks SOF/VEL x 12 weeks LDV/SOF X 12 weeks	N/A
1	***Experienced (prior NS5A-containing regimen)***	***Non-cirrhotic or compensated cirrhosis***	SOF/VEL/VOX x 12 weeks-24 weeks	SOF/VEL/VOX x 12 weeks	N/A
2	***Naïve***	***Non-cirrhotic***	SOF/VEL x 12 weeks G/P x 8 weeks	SOF/VEL x 12 weeks G/P x 8 weeks	SOF + RBV X 12 weeks
2		***Cirrhotic***	SOF/VEL +/- x 12 weeks	SOF/VEL x 12 weeks G/P x 12 weeks	SOF + RBV x 16 weeks
2		***Decompensated***	SOF/VEL + RBV x 12 weeks	SOF/VEL + RBV x 12 weeks DCV/SOF + RBV x 12 weeks	SOF + RBV x 16 weeks
2	***Experienced (prior PEG-IFN/RBV)***	***Non-cirrhotic or Compensated Cirrhotic***	SOF/VEL x 12 weeks G/P x 8-12 weeks	SOF/VEL x 12 weeks G/P x 8-12 weeks	N/A
2	***Experienced (NS5A-experienced)***	***Non-cirrhotic or compensated cirrhosis***	SOF/VEL/VOX x 12 weeks – 24 weels	SOF/VEL/VOX x 12 weeks	N/A
2	***Experienced (SOF + RBV)***	***Non-cirrhotic or Compensated Cirrhotic***	SOF/VEL x 12 weeks G/P x 8-12 weeks	SOF/VEL x 12 weeks G/P x 12 weeks	N/A
3	***Naïve***	***Non-cirrhotic***	G/P x 8 weeks SOF/VEL X 12 weeks	G/P x 8 weeks SOF/VEL X 12 weeks	DCV/SOF X 12 weeks
3		***Compensated Cirrhotic***	SOF/VEL x 12 weeks G/P x 12 weeks	SOF/VEL x 12 weeks G/P x 12 weeks	DCV/SOF + RBV x 12 weeks
3		***Decompensated Cirrhosis***	SOF/VEL + RBV X 12 weeks	SOF/VEL + RBV x 12 weeks DCV/SOF + RBV x 12 weeks	N/A
3	***Experienced (prior PEG-IFN/RBV only)***	***Non-cirrhotic***	G/P x 16 weeks	SOF/VEL x 12 weeks	N/A

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3		***Compensated Cirrhotic***	G/P x 16 weeks	SOF/VEL/VOX x 12 weeks EBV/GZR + SOF x 12 weeks	DCV/SOF + RBV x 24 weeks
3	***Experienced (NS5A or SOF)***	***Non-cirrhotic or Compensated Cirrhotic***	SOF/VEL/VOX x 12 weeks	SOF/VEL/VOX x 12 weeks	N/A
4	***Naïve***	***Non-cirrhotic***	EBV/GZR x 12 weeks LDV/SOF x 12 weeks SOF/VEL x 12 weeks G/P x 8 weeks	EBV/GZR x 12 weeks LDV/SOF x 12 weeks SOF/VEL x 12 weeks G/P x 8 weeks	DCV/SOF x 12 weeks LDV/SOF x 12 weeks
4		***Compensated Cirrhotic***	EBV/GZR x 12 weeks LDV/SOF x 12 weeks SOF/VEL x 12 weeks G/P x 12 weeks	EBV/GZR x 12 weeks LDV/SOF x 12 weeks SOF/VEL x 12 weeks G/P x 12 weeks	DCV/SOF x 24 weeks DCV/SOF + RBV x 12 weeks LDV/SOF x 24 weeks LDV/SOF + RBV x 12 weeks
4		***Decompensated Cirrhosis***	LDV/SOF + RBV x 12 weeks SOF/VEL + RBV x 12 week	LDV/SOF + RBV x 12 weeks SOF/VEL + RBV x 12 week DCV/SOF + RBV X 12 week	N/A
4	***Experienced (prior PEG-IFN/RBV only)***	***Non-cirrhotic or Compensated Cirrhotic***	N/A	SOF/VEL x 12 weeks EBV/GZR x 12 weeks LDV/SOF x 12 weeks G/P x 8 -12 weeks	N/A
	Experienced (SOF)	***Non-cirrhotic or compensated cirrhotic***	G/P x 8-12 weeks SOF/VEL x 12 weeks	SOF/VEL/VOX x 12 weeks	N/A
	Experienced (NS5A)	***Non-cirrhotic or compensated cirrhotic***	SOF/VEL/VOX x 12 weeks	SOF/VEL/VOX x 12 weeks	
5/6	***Naïve or Experienced (prior PEG-IFN/RBV only)***	***Non-cirrhotic or Compensated Cirrhotic***	N/A	SOF/VEL x 12 weeks LDV/SOF x 12 weeks G/P x 8-12 weeks	LDV/SOF X 12 weeks
5/6	***Experienced (NS5A or SOF)***	***Non cirrhotic or Compensated Cirrhotic***	N/A	SOF/VEL/VOX x 12 weeks	N/A

**No baseline NS5A RAVs. Abbreviations: CTP = Child-Turcotte-Pugh; DAA = direct acting antiviral; DCV = daclatasvir; EBV/GZR = elbasvir/grazoprevir; G/P = glecaprevir/pibrentasvir, LDV/SOF = ledipasvir/sofosbuvir; OMB/PTV-R + DAS = ombitasvir, paritaprevir and ritonavir with dasabuvir; PEG-IFN = pegylated interferon; VEL/SOF = velpatasvir/sofosbuvir; RAP = resistance-associated polymorphisms; RAV = resistance-associated variant; RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir; SOF/VEL/VOX = sofosbuvir, velpatasvir, voxilaprevir

New Formulations or Indications:
None identified

Two combination treatments (OMB/PTV-R + DAS [Viekira Pak®/Viekira XR®] and OMB/PTV-R [Technivie®]) have been discontinued by Abbvie Pharmaceuticals. Both agents are expected to be available through January 2019.

New FDA Safety Alerts:
None identified

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Randomized Controlled Trials:

A total of 49 citations were manually reviewed from the initial literature search. After further review, 46 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical). The remaining 3 trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 2. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Toyoda, 2018[36]	G/P for 8 weeks vs. 12 weeks of SOF + RBV	HCV G2 patients without cirrhosis or compensated cirrhosis (n=11) in Japan (n=136)	SVR12	SVR12: G/P: 88/90 (97.8%) SOF + RBV: 43/46 (93.5%)
Tam, 2017[37] RESCUE	GT 1 or GT 4: 1. LDV/SOF +/- RBV x 12 weeks vs. 2. LDV/SOF x 24 weeks GT 1 with HIV: 3. LDV/SOF + RBV x 12 weeks vs. 4. LDV/SOF X 24 weeks	SOF-experienced, NS5a treatment naïve 1: HCV G1 or G4 2: HCV G1 with HIV coinfection	SVR12	SVR12: *HCV G1 or G4 (non-cirrhotic):* 1. 13/16 (81%) 2. 17/18 (100%) *HCV G1 or G4 (cirrhotic):* 1. 20/25 (80%) 2. 22/24 (92%) *HIV coinfection:* 3. 4/4 (100%) 4. 3/3 (100%)
Foster, 2018[22]	Treatment-naïve: 1. EBR/GZR + SOF + RBV x 8 weeks vs. 2. EBR/GZR + SOF x 12 weeks Treatment-experienced: 3. EBR/GZR + SOF +/- RBV X 12 weeks vs. 4. EBR/GZR + SOF x 16 weeks	HCV GT 3, compensated cirrhosis with HCV RNA $\geq$ 10,000 IU/ml	SVR 12	SVR12: *Treatment-naïve:* 1. 21/23 (91%) 2. 23/24 (96%) *Treatment-experienced:* 3. 17/18 (94%) 4. 17/18 (100%)

Abbreviations: RCT = EBR/GZR: elbasvir/grazoprevir; GT: genotype; HCV: hepatitis C virus; G/P: glecaprevir/pibrentasvir; LDV/SOF: ledipasvir/sofosbuvir; SOF: sofosbuvir; SVR12: sustained viral response at week 12; RBV: ribavirin

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Evidence for DAA use in substance use disorder and PWID:
Injection drug use is a significant risk factor for HCV-related disease and transmission, as well as for all-cause morbidity and mortality. The biggest risk factor for infection with HCV is sharing needles and/or syringes.[3] The current OHP prior authorization policy allows treatment for HCV for PWID. If the provider is aware of current illicit injectable drug use, the patient must be enrolled in a treatment program under the care of an addiction or substance use specialist. Current guidelines recommend that recent and active drug use should not be seen as an absolute contraindication to HCV therapy. The guidelines also recommend that PWID should be offered harm reduction services when available, including needle/syringe service programs and substance use disorder treatment programs.

A recent Cochrane systematic review evaluated the effects of needle syringe programs and opioid substitution therapy for preventing transmission of HCV among PWID.[3] A literature search for RCTs, cohort studies and case-control studies was conducted. The primary outcome was HCV incidence. Overall, 28 observational studies were identified for inclusion. No RCTs were identified. The majority of the studies were prospective cohort studies that evaluated opioid substitution therapy with methadone or buprenorphine. Twelve studies were judged to be at moderate risk of bias due to confounding and 12 studies to be at high risk of bias because confounding was insufficiently addressed. Four studies were at critical risk of bias because they did not make any adjustment for confounding. Overall, there was very low evidence that needle exchange program coverage did not reduce HCV acquisition (RR 0.79; 95% CI 0.39 to 1.61) with high heterogeneity. There was low quality evidence that combined needle exchange program coverage and opioid substitution therapy did result in a decreased rate of HCV acquisition (RR 0.29; 95% CI 0.07 to 0.89) which was more pronounced than with opioid substitution therapy alone (RR 0.50; 95% CI 0.40 to 0.63) compared to no opioid substitution therapy. Although the effect size is strong, conclusions based on observational data only should not be made and further RCTs should be conducted in this patient population.

The following clinical trials were identified evaluating treatment of HCV in PWID or alcohol use disorder. Overall, randomized prospective data is limited. Most studies enroll patients receiving treatment for injection drug use with opioid substation therapy. The trial by Norton, et al. had one small arm (n=10) of patients actively using drugs not receiving opioid substation therapy and nine of the ten patients achieved SVR12. [38] There is an ongoing randomized trial in 150 PWID with chronic HCV evaluating three models of care for HCV therapy delivered in an opioid substitution treatment program and their effects on adherence and virological outcomes.[39]

Study	Comparison	Population	Primary Outcome	Results
Norton, 2017[38] Observational cohort study	1. no active or history of drug use 2. no active drug use, receiving OAT 3. active drug use, not on OAT 4. active drug use, on OAT	Patients who received HCV treatment in a primary care clinic in the Bronx, NY (n=89)	SVR12	SVR12: 1. 41/43 (95%) 2. 15/15 (100%) 3. 9/10 (90%) 4. 20/21 (95%)
Grebely, 2018[40] SIMPLIFY	SOF/VEL x 12 weeks	HCV GT 1-6 with recent injection drug use (past 6 months) (n=103); 57% receiving OST	SVR12	SVR12: 97/103 (94%)

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Open-label, single arm, phase 4				
Dore, 2017[41] C-EDGE CO-STAR RCT, DB, PC	EBR/GZR (immediate treatment group [ITG] vs. deferred treatment group [DTG]) DTG: 12wks placebo + 4 weeks de-randomization + 12 weeks treatment	HCV GT 1, GT 4 or GT 6, treatment naïve, receiving OAT with methadone or buprenorphine	SVR12	SVR12: ITG: 184/201 (91.5%) DTG: 85/95 (89.5%) SVR24: ITG: 170/201 (84.6%) DTG: 81/95 (85.3%)

Abbreviations: DB = double blind; EBR/GZR: elbasvir/grazoprevir; GT = genotype; HCV: hepatitis C virus; OAT = opioid agonist therapy; PC = placebo controlled; RCT = randomized controlled trial; SVR12: sustained viral response at week 12; SOF/VEL: sofosbuvir/velpatasvir

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36. Toyoda H, Chayama K, Suzuki F, et al. Efficacy and safety of glecaprevir/pibrentasvir in Japanese patients with chronic genotype 2 hepatitis C virus infection. *Hepatology (Baltimore, Md).* 2017.
37. Tam E, Luetkemeyer AF, Mantry PS, et al. Ledipasvir/sofosbuvir for treatment of hepatitis C virus in sofosbuvir-experienced, NS5A treatment-naive patients: Findings from two randomized trials. *Liver international : official journal of the International Association for the Study of the Liver.* 2018;38(6):1010-1021.
38. Norton BL, Fleming J, Bachhuber MA, et al. High HCV cure rates for people who use drugs treated with direct acting antiviral therapy at an urban primary care clinic. *The International journal on drug policy.* 2017;47:196-201.
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40. Grebely J, Dalgard O, Conway B, et al. Sofosbuvir and velpatasvir for hepatitis C virus infection in people with recent injection drug use (SIMPLIFY): an open-label, single-arm, phase 4, multicentre trial. *The lancet Gastroenterology & hepatology.* 2018;3(3):153-161.
41. Dore GJ, Altice F, Litwin AH, et al. Elbasvir-Grazoprevir to Treat Hepatitis C Virus Infection in Persons Receiving Opioid Agonist Therapy: A Randomized Trial. *Annals of internal medicine.* 2016;165(9):625-634.

Appendix 1: Current Preferred Drug List

Route	Formulation	Brand	Generic	PDL
ORAL	TABLET	EPCLUSA	sofosbuvir/velpatasvir	Y
ORAL	TABLET	ZEPATIER	elbasvir/grazoprevir	Y
ORAL	TABLET	MAVYRET	glecaprevir/pibrentasvir	Y
ORAL	TABLET	VOSEVI	sofosbuvir/velpatas/voxilaprev	Y
ORAL	TABLET	DAKLINZA	daclatasvir dihydrochloride	N
ORAL	TABLET	DAKLINZA	daclatasvir dihydrochloride	N
ORAL	TABLET	DAKLINZA	daclatasvir dihydrochloride	N
ORAL	TABLET	HARVONI	ledipasvir/sofosbuvir	N
ORAL	TAB DS PK	VIEKIRA PAK	ombita/paritap/riton/dasabuvir	N
ORAL	TAB BP 24H	VIEKIRA XR	ombita/paritap/riton/dasabuvir	N
ORAL	TABLET	TECHNIVIE	ombitasvir/paritaprev/ritonav	N
ORAL	TABLET	SOVALDI	sofosbuvir	N

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Appendix 2: Abstracts of Comparative Clinical Trials

1. Toyoda H, Chayama K, Suzuki F, Sato K, et al. Efficacy and safety of glecaprevir/pibrentasvir in Japanese patients with chronic genotype 2 hepatitis C virus infection. Hepatology. 2017 Sep 2. doi: 10.1002/hep.29510. [Epub ahead of print]

Glecaprevir (nonstructural protein 3/4A protease inhibitor) and pibrentasvir (nonstructural protein 5A inhibitor) (G/P), a coformulated once-daily, all oral, ribavirin (RBV)-free, direct-acting antiviral regimen, was evaluated for safety and efficacy in hepatitis C virus genotype 2 (GT2)-infected Japanese patients, including those with compensated cirrhosis. CERTAIN-2 is a phase 3, open-label, multicenter study assessing the safety and efficacy of G/P (300/120 mg) once daily in treatment-naive and interferon ± RBV treatment-experienced Japanese patients without cirrhosis but with GT2 infection. Patients were randomized 2:1 to receive 8 weeks of G/P (arm A) or 12 weeks of sofosbuvir (400 mg once daily) + RBV (600-1000 mg weight-based, twice daily) (arm B). The primary endpoint was noninferiority of G/P compared to sofosbuvir + RBV by assessing sustained virologic response at posttreatment week 12 (SVR12) among patients in the intent-to-treat population. SVR12 was also assessed in treatment-naive and interferon ± RBV treatment-experienced patients with GT2 infection and compensated cirrhosis who received G/P for 12 weeks in the CERTAIN-1 study. A total of 136 patients were enrolled in CERTAIN-2. SVR12 was achieved by 88/90 (97.8%) patients in arm A and 43/46 (93.5%) patients in arm B. No patient in arm A experienced virologic failure, while 2 did in arm B. The primary endpoint was achieved. In CERTAIN-1, 100% (18/18) of GT2-infected patients with compensated cirrhosis achieved SVR12. Treatment-emergent serious adverse events were experienced by 2 patients without cirrhosis in each arm and no patient with cirrhosis.

2.. Tam E, Luetkemeyer AF, Mantry PS, Satapathy SK, Ghali P, Kang M, RESCUE and ACTG A5348 study investigators. Ledipasvir/sofosbuvir for treatment of hepatitis C virus in sofosbuvir-experienced, NS5A treatment-naïve patients: Findings from two randomized trials. Liver Int. 2018 Jun;38(6):1010-1021. doi: 10.1111/liv.13616. Epub 2017 Dec 5.

BACKGROUND & AIMS:
We report data from two similarly designed studies that evaluated the efficacy, safety, and optimal duration of ledipasvir/sofosbuvir (LDV/SOF) ± ribavirin (RBV) for retreatment of chronic hepatitis C virus (HCV) in individuals who failed to achieve sustained virological response (SVR) with prior SOF-based, non-NS5A inhibitor-containing regimens.
METHODS:
The RESCUE study enrolled HCV mono-infected adults with genotype (GT) 1 or 4. Non-cirrhotic participants were randomized to 12 weeks of LDV/SOF or LDV/SOF + RBV. Compensated cirrhotic participants were randomized to LDV/SOF + RBV (12 weeks) or LDV/SOF (24 weeks). The AIDS Clinical Trials Group A5348 study randomized genotype 1 adults with HCV/HIV co-infection to LDV/SOF + RBV (12 weeks) or LDV/SOF (24 weeks). Both studies used SVR at 12 weeks post-treatment (SVR12) as the primary endpoint.
RESULTS:
In the RESCUE study, 82 participants were randomized and treated, and all completed treatment. Overall, SVR12 was 88% (72/82); 81-100% in non-cirrhotic participants treated with LDV/SOF or LDV/SOF + RBV for 12 weeks and 80-92% in cirrhotic participants treated with LDV/SOF + RBV for 12 weeks or LDV/SOF for

24 weeks. Adverse events (AEs), mostly mild-to-moderate in severity, were experienced by 78% of participants, with headache and fatigue most frequently reported. One serious AE, not related to treatment, was observed. No premature discontinuations of study drug, or deaths occurred. In the A5348 study, seven participants were randomized (cirrhotic n = 1; GT1a n = 5) and all attained SVR12, with no serious AEs or premature discontinuations.
CONCLUSIONS:
In this SOF-experienced, NS5A inhibitor-naïve population, which included participants with cirrhosis or HCV/HIV co-infection, high SVR12 rates were achieved.

3. Foster GR, Agarwal K, Cramp ME, Moreea S, et al. Elbasvir/grazoprevir and sofosbuvir for hepatitis C virus genotype 3 infection with compensated cirrhosis: A randomized trial. Hepatology. 2018 Jun;67(6):2113-2126. doi: 10.1002/hep.29852. Epub 2018 Apr 19.

Abstract
Many direct-acting antiviral regimens have reduced activity in people with hepatitis C virus (HCV) genotype (GT) 3 infection and cirrhosis. The C-ISLE study assessed the efficacy and safety of elbasvir/grazoprevir (EBR/GZR) plus sofosbuvir (SOF) with and without ribavirin (RBV) in compensated cirrhotic participants with GT3 infection. This was a phase 2, randomized, open-label study. Treatment-naive participants received EBR/GZR + SOF + RBV for 8 weeks or EBR/GZR + SOF for 12 weeks, and peginterferon/RBV treatment-experienced participants received EBR/GZR + SOF ± RBV for 12 weeks or EBR/GZR + SOF for 16 weeks. The primary endpoint was HCV RNA <15 IU/mL 12 weeks after the end of treatment (sustained virologic response at 12 weeks [SVR12]). Among treatment-naive participants, SVR12 was 91% (21/23) in those treated with RBV for 8 weeks and 96% (23/24) in those treated for 12 weeks. Among treatment-experienced participants, SVR12 was 94% (17/18) and 100% (17/17) in the 12-week arm, with and without RBV, respectively, and 94% (17/18) in the 16-week arm. Five participants failed to achieve SVR: 2 relapsed (both in the 8-week arm), 1 discontinued due to vomiting/cellulitis (16-week arm), and 2 discontinued (consent withdrawn/lost to follow-up). SVR12 was not affected by the presence of resistance-associated substitutions (RASs). There was no consistent change in insulin resistance, and 5 participants reported serious adverse events (pneumonia, chest pain, opiate overdose, cellulitis, decreased creatinine). High efficacy was demonstrated in participants with HCV GT3 infection and cirrhosis. Treatment beyond 12 weeks was not required, and efficacy was maintained regardless of baseline RASs.
CONCLUSION:
Data from this study support the use of EBR/GZR plus SOF for 12 weeks without RBV for treatment-naive and peginterferon/RBV-experienced people with GT3 infection and cirrhosis

Appendix 3: Medline Search Strategy

▼ **Search History** (32)

# ▲	Searches	Results
1	glecaprevir.mp.	14
2	pibrentasvir.mp.	17
3	mavyret.mp.	1
4	sofosbuvir.mp. or SOFOSBUVIR/	1299
5	velpatasvir.mp.	79
6	voxilaprevir.mp.	21
7	vosevi.mp.	1
8	epclusa.mp.	5
9	daclatasvir.mp.	504
10	daklinza.mp.	10
11	technivie.mp.	3
12	ombitasvir.mp.	249
13	paritaprevir.mp.	239
14	ritonavir.mp. or RITONAVIR/	5766
15	dasabuvir.mp.	225
16	simeprevir.mp. or SIMEPREVIR/	534
17	ledipasvir.mp.	482
18	harvoni.mp.	35

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☐	19	antiviral agents.mp. or Antiviral Agents/	72769
☐	20	direct acting antivirals.mp.	1150
☐	21	protease inhibitors.mp. or Protease Inhibitors/	40950
☐	22	ribavirin.mp. or RIBAVIRIN/	14116
☐	23	ns5a inhibitors.mp.	181
☐	24	ns5b inhibitor.mp.	78
☐	25	Hepatitis C, Chronic/ or Hepatitis C/	58411
☐	26	hepatocellular carcinoma.mp. or Carcinoma, Hepatocellular/	88176
☐	27	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	116755
☐	28	25 or 26	140262
☐	29	27 and 28	19471
☐	30	limit 29 to (english language and humans and yr="2017 -Current" and (clinical trial, phase iii or clinical trial, phase iv or comparative study or controlled clinical trial or meta analysis or practice guideline or randomized controlled trial or systematic reviews))	184
☐	31	from 30 keep 13-14, 18, 22-23, 28, 34, 36-39...	49
☐	32	from 31 keep 2-3, 5, 7, 9-10, 12-13, 15...	25

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Appendix 4: Prior Authorization Criteria

Hepatitis C Direct-Acting Antivirals

Goals:

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

Length of Authorization:

- 8-16 weeks

Requires PA:

- All direct-acting antivirals for treatment of Hepatitis C

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for treatment of chronic Hepatitis C infection?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is expected survival from non-HCV-associated morbidities more than 1 year?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.

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Approval Criteria		
4. Has all of the following pre-treatment testing been documented: a. Genotype testing in past 3 years; b. Baseline HCV RNA level in past 6 months; c. Current HIV status of patient d. Current HBV status of patient e. Pregnancy test in past 30 days for a woman of child-bearing age; and f. History of previous HCV treatment and outcome? Note: Direct-acting antiviral agents can re-activate hepatitis B in some patients. Patients with history of HBV should be monitored carefully during and after treatment for flare-up of hepatitis. Prior to treatment with a DAA, all patients should be tested for HBsAG, HBsAb, and HBcAB status.	**Yes:** Record results of each test and go to #5 Note: If the patient has HIV or HBV co-infection, it is highly recommended that a specialist be consulted prior to treatment. Currently treatment is not recommended during pregnancy due to lack of safety and efficacy data	**No**: Pass to RPh. Request updated testing.
5. Which regimen is requested?	Document and go to #6	
6. Does the patient have HIV coinfection and is under treatment by a specialist with experience in HIV? Note: persons with HIV/HCV coinfection are at risk for rapidly progressing fibrosis	**Yes:** Go to #101 ~~1~~	**No:** Go to #7

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Approval Criteria		
7. Does the patient have: a) A biopsy, imaging test (transient elastography [FibroScan®], acoustic radiation force impulse imaging [ARFI], or shear wave elastography [SWE]) to indicate portal fibrosis with septa (METAVIR F2) advanced fibrosis (METAVIR F3) or cirrhosis (METAVIR F4); **OR** Clinical, radiologic or laboratory evidence of complications of cirrhosis (ascites, portal hypertension, hepatic encephalopathy, hepatocellular carcinoma, esophageal varices)?	**Yes:** Go to #10 Note: Other imaging and blood tests are not recommended based on evidence of poor sensitivity and specificity compared to liver biopsy. However, if imaging testing is not regionally available, a serum test (FIBROSpect II; Fibrometer; enhanced liver fibrosis [ELF], Fibrosure) can be used to confirm METAVIR F2 or greater but cannot be used for denial. For results falling in a range (e.g. F1 to F2), fibrosis stage should be categorized as the higher F stage for the purpose of treatment, or require one additional, more specific test (per HERC AUROC values http://www.oregon.gov/OHA/HPA/CSI-HERC/Pages/Evidence-based-Reports-Blog.aspx?View=%7b2905450B-49B8-4A9B-AF17-5E1E03AB8B6B%7d&SelectedID=237) to be obtained to determine the stage of fibrosis. However, additional testing cannot be limited to biopsy. After one additional test, if a range still exists, the highest F score in the range will be used for determining coverage.	**No:** Go to #8

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Approval Criteria		
8. Does the patient have one of the following extrahepatic manifestations of Hepatitis C? ~~(with documentation from a relevant specialist that their condition is related to HCV)?~~ a) Lymphoproliferative disease, including type 2 or 3 cryoglobulinemia with end-organ manifestations (i.e., leukocytoclastic vasculitis); or b) Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis; or c) Porphyria cutanea tarda or lichen planus d) Lymphomas (B-cell non-Hodgkin lymphoma) e) Type 2 Diabetes	**Yes:** Go to #10	**No:** Go to #9
9. Is the patient in one of the following transplant settings: a) Listed for a transplant and treatment is essential to prevent recurrent hepatitis C infection post-transplant; or b) Post solid organ transplant?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness.
10. If METAVIR F4: Is the regimen prescribed by, or in consultation with, a hepatologist, gastroenterologist, or infectious disease specialist? **OR** If METAVIR F3: Is the regimen prescribed by, OR is the patient in the process of establishing care with or in consultation with a hepatologist, gastroenterologist, or infectious disease specialist? **OR** If METAVIR ≤F2: The regimen does not need to be prescribed by or in consultation with a specialist.	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness. Forward to DMAP for further manual review to determine appropriateness of prescriber.

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Approval Criteria		
~~11. In the previous 6 months:~~ ~~a) Does the patient actively abuse alcohol (>14 drinks per week for men or >7 drinks per week for women or binge alcohol use (>4 drinks per occasion at least once a month); OR~~ ~~b) Has the patient been diagnosed with a substance use disorder; OR~~ ~~c) Is the prescriber aware of current alcohol abuse or illicit injectable drug use?~~	~~**Yes:** Go to #12~~	~~**No:** Go to #13~~
~~12. Is the patient enrolled in a treatment program under the care of an addiction/substance use treatment specialist?~~	~~**Yes:** Go to #13~~	~~**No:** Pass to RPh. Deny; medical appropriateness.~~
~~13.~~11. Is there attestation that ~~Will~~ the patient and provider will comply with all case management interventions to promote the best possible outcome for the patient and adhere to monitoring requirements required by the Oregon Health Authority, including measuring and reporting of a post-treatment viral load?	**Yes**: Go to #1~~2~~4	**No:** Pass to RPh. Deny; medical appropriateness.
~~14.~~12. Is the prescribed drug: a) Elbasvir/grazoprevir for GT 1a infection; or b) Daclatasvir + sofosbuvir for GT 3 infection?	**Yes**: Go to #1~~3~~5	**No:** Go to #1~~4~~6
~~15.~~13. Has the patient had a baseline NS5a resistance test that documents a resistant variant to one of the agents in #16? Note: Baseline NS5A resistance testing is required.	**Yes:** Pass to RPh; deny for appropriateness	**No:** Go to #1~~4~~6 Document test and result.

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Approval Criteria		
~~16.~~14. Is the prescribed regimen include a NS3/4a protease inhibitor (elbasvir, glecaprevir, simeprevir, paritaprevir, voxilaprevir)?	**Yes:** Go to #1~~57~~	**No:** Go to #1~~68~~
~~17.~~15. Does the patient have moderate-severe hepatic impairment (Child-Pugh B or Child-Pugh C)?	**Yes:** Pass to RPh; deny for appropriateness	**No:** Go to #1~~68~~
~~18.~~16. Is the prescribed regimen for the retreatment after failure of a DAA due to noncompliance or lost to follow-up?	**Yes:** Pass to RPh; Deny and refer to medical director for review	**No:** Go to #1~~79~~
~~19.~~17. Is the prescribed drug regimen a recommended regimen based on the patient's genotype, treatment status (retreatment or treatment naïve) and cirrhosis status (see **Table 1**)?	**Yes:** Approve for 8-16 weeks based on duration of treatment indicated for approved regimen	**No:** Pass to RPh. Deny; medical appropriateness.

P&T Review: *9/18 (MH); 9/17; 9/16; 1/16; 5/15; 3/15; 1/15; 9/14; 1/14*
Implementation: *TBD; 1/1/2018; 2/12/16; 4/15; 1/15*

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Policy Evaluation: Benzodiazepines

Research Questions:

1. Has the proportion of patients receiving benzodiazepines for long-term use (more than 4 weeks every 4 months) decreased since implementation of the prior authorization (PA) criteria?
2. Are there any subgroups of patients based on drug therapy, patient characteristics (i.e. coordinated care organization [CCO] enrollment, age, or mental health diagnosis), concurrent medications (sedating therapy, antidepressant, or antipsychotic use), or prescriber characteristics (i.e. provider specialty) who more commonly receive long-term therapy beyond 4 weeks?
3. For patients on long-term therapy, what proportion of patients had a change in benzodiazepine treatment (i.e. treatment discontinuation, change in medication, increase in dose, or decrease in dose) after implementation of the policy?
4. Has there been a change in emergency department (ED) visits, hospitalizations, benzodiazepine overdose, or sedative overdoses since implementation of the PA criteria?
5. Did members have an increased number of hospitalizations or ED visits following a denied benzodiazepine claim?

Conclusions:

1. After implementation of the policy, there were fewer patients prescribed long-term benzodiazepine therapy.
    a. Before implementation of the policy, approximately 56% of the patients newly started on benzodiazepines were prescribed benzodiazepines for greater than 30 days compared to 42% after implementation of the policy.
    b. The number of new start patients who transitioned to continuous benzodiazepine therapy (represented by a proportion of days covered [PDC] >75%) decreased from 8.7% to 2.6%, and patients with PDC of 26-75% (representing intermittent therapy) decreased from 28% to 19%.
    c. Similarly, there was a slight decrease in the number of patients on long-term therapy with subsequent claims associated with benzodiazepine poisoning, accidental poisoning, or benzodiazepine-related adverse effects (**Figure 2**). However, rates of overall poisoning from any sedative were relatively unchanged (**Figure 3**).
2. Subgroup analyses based on patient characteristics, concurrent medications, and prescriber characteristics
    a. Overall demographics for patients prescribed short-term and long-term benzodiazepine use were similar. Benzodiazepines are most commonly prescribed for adults (88%) and for female members (69%).
    b. Patients with a history of long-term benzodiazepine use had more medical claims associated with mental health diagnoses (90%) compared to patients with short-term use (84%). Similarly, compared to patients who were treatment naïve, patients with a history of long-term benzodiazepine use had more frequent utilization of selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs; 50%), other antidepressants (29%), and second generation antipsychotics (23-24%). Overall, utilization for mental health drugs was similar before and after implementation of the policy.

c. Overall, benzodiazepines (for any duration of therapy) are most commonly prescribed by general practitioners including family practitioners, internists, physician assistants, and family nurse practitioners. Specialists in mental health (psychiatrists and psychiatric mental health nurse practitioners) were more likely to prescribe long-term benzodiazepine therapy.

3. In patients with a history of long-term benzodiazepine use, approximately 23-26% of patients had a change in benzodiazepine drug or dose based on claims history, and approximately 9.5% of patients with long-term benzodiazepine use had a denied benzodiazepine claim. Of the patients with a denied claim, 58% had a subsequent paid claim within the next 30 days indicating that a prior authorization was submitted for these patients. Another 20% of patients had a paid benzodiazepine claim within 90 days of the initial denial.
4. Overall, there was no change in rate of hospitalization or ED visits upon comparison of rates before and after implementation of the policy. For patients with a history of short-term use, rates of hospitalization and emergency department visits were maintained at 4.5% and 22%, respectively. Overall rates of hospitalization and ED visits also remained unchanged for patients on long-term benzodiazepine therapy after implementation of the policy (2% and 12%, respectively).
5. For members included in the analysis, only 7.2% of hospitalizations and 8.8% of ED visits occurred following a denied benzodiazepine claim. In patients defined as having a history of long-term benzodiazepine use, only 6% of ED visits and hospitalizations occurred after a denied benzodiazepine claim, and the majority of medical visits occurred following paid claims for a benzodiazepine (80% of ED visits and hospitalizations).

Recommendation:

- Update PA criteria for benzodiazepines (**Appendix 3**).

Background:

Benzodiazepines are commonly prescribed in Oregon for a variety of mental health conditions. The United States Food and Drug Administration (FDA) labeled indications for benzodiazepines include anxiety, panic disorder, alcohol withdrawal, and seizures. Some benzodiazepines such as lorazepam are also FDA indicated for insomnia, and they can be used off-label for schizophrenia, depression, acute stress disorders, agitation, or bipolar disorder.

A recent Drug Effectiveness Review Project (DERP) report documented the limited evidence for long-term treatment with benzodiazepines.[1] Available evidence was often limited to less than 8 weeks of treatment, and even evidence supporting short-term efficacy compared to alternative treatments was of poor quality.[1] For the treatment of panic disorder, post-traumatic stress disorder (PTSD), and depression, the majority of evidence compared benzodiazepines to tricyclic antidepressants (TCAs). There was low quality evidence that benzodiazepines had statistically improved response rates compared to TCAs (RR 1.13; 95% CI 1.01 to 1.27) for panic disorder, but there was insufficient evidence to support treatment for other conditions.[1] Similarly, there was insufficient evidence to compare effectiveness of benzodiazepines to selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs), and recently updated guidelines from the Veterans Administration and Department of Defense recommend against the use of benzodiazepines (as monotherapy or combination therapy) for treatment of PTSD.[2] For the treatment of general anxiety disorder, there was low quality evidence of no difference in treatment response between antidepressants (SSRIs, SNRIs, or TCAs) and benzodiazepines over 4 to 8 weeks.[1] Compared to patients treated with TCAs, fewer patients treated with benzodiazepines for anxiety discontinued treatment though the reasons for treatment discontinuation were not reported.[1] Similarly, evidence for the treatment of schizophrenia was limited to comparisons with older antipsychotics (primarily haloperidol and chlorpromazine) with insufficient evidence to determine differences in efficacy between these agents.

In addition, there is low quality evidence from observational studies to indicate that concomitant use of benzodiazepines and opioid medications may be associated with increased risk of death.[1] Due to the retrospective nature of these data, the exact risk associated with concomitant benzodiazepines and opioids

is unclear. However, because of the concerning nature of these trends, FDA labeling for all benzodiazepines has been updated with a boxed warning detailing the risk of profound sedation, respiratory depression, coma and death associated with concomitant use of benzodiazepines and opioids.[3]

In Oregon, the majority of benzodiazepines (with the exception of sedative benzodiazepines and clonazepam) are classified as carve-out medications and are paid for by fee-for-service (FFS), unlike physical health drugs which are paid by the patient's CCO. In the second quarter of 2017 (4/1/17 to 7/31/17), over 18,800 patients had more than 31,000 claims for a benzodiazepine listed in **Appendix 2**. Sedative benzodiazepines for the treatment of sleep disorders (including triazolam and temazepam) are managed under separate PA criteria which ensure therapy is prescribed for funded indications, for appropriate duration, and not prescribed in combination with other sedating medications. All other oral benzodiazepines are managed by the PA criteria in **Appendix 1**. These criteria were implemented in July 2016 for patients receiving benzodiazepines for a duration longer than 4 weeks. The primary goal of the policy was to decrease the proportion of patients on inappropriate long-term benzodiazepine therapy with the hope that it would prevent adverse effects associated with long-term benzodiazepine use. Secondary goals of this evaluation include assessment of unintentional harms including hospitalizations and ED visits as a result of this policy and identification of areas for policy improvement. Due to the large volume of patients in the population who utilize benzodiazepines, the PA focused on targeting patients newly started on a benzodiazepine. Any patient who had a claim for a benzodiazepine in the 2 months prior to implementation of the policy (including new start patients and patients on long-term therapy) were grandfathered by implementing long-term PAs for their current therapy. Patients impacted by this policy included FFS patients prescribed benzodiazepines (excluding sedative benzodiazepines such as triazolam or temazepam) or patients enrolled in a CCO who received a carve-out benzodiazepine (including lorazepam, diazepam, alprazolam, oxazepam, or chlordiazepoxide) beyond 4 weeks. In addition, this policy may occasionally apply to patients on chronic therapy if they are new to Oregon Health Plan (OHP) or were originally grandfathered but have a change in drug or dose. Short-term use of benzodiazepines (4 weeks every 4 months) does not require a PA. Long-term therapy can be approved for the following diagnoses: diagnosis of malignant neoplasm or other end of life diagnosis, diagnosis of epilepsy, or an OHP-funded diagnosis with clinical rationale to support long-term benzodiazepine use. OHP funded indications are only approved if the patient also meets the following criteria: no history of substance abuse and no concurrent sedative, hypnotic, or opioid use. Prior to implementation of the policy, both providers and pharmacies were notified of these changes in OHP policy.

Methods:

This uncontrolled before-and-after analysis compared utilization of benzodiazepines in a historical control group of patients before the implementation of the PA (from 7/1/15 to 6/30/16) to patients after implementation of the policy (from 7/1/16 to 6/30/17). The analysis was divided into 2 distinct populations: patients were treatment naïve or on short-term benzodiazepine therapy (≤30 days in the 120 days prior to the index event [IE]) and patients who were on chronic benzodiazepine therapy (>30 days in the 120 days prior to the IE). In order to avoid counting patients multiple times over the same period, the IE was defined as the first denied or paid FFS claim for greater than 5 days' supply for a benzodiazepine within the each reporting period. If a patient had multiple claims for a benzodiazepine within this time frame, the first claim in the reporting period (the index event) was used to classify the patient according to paid or denied status. Any subsequent paid or denied benzodiazepine claims for a patient were evaluated to calculate days' supply but were not generally evaluated for status (paid or denied). Patients with only claims for 1-5 days were excluded as these patients were likely prescribed benzodiazepines for pre-procedure or urgent use only. Denied claims were defined as claims with an error code of 6507 ("Pharmacy Policy – Benzodiazepine Limits") and without any of the error codes listed in **Appendix 3**. Baseline characteristics and CCO enrollment were assessed at time of the IE.

Chronic (or long-term) therapy was defined as greater than 30 days of treatment in the 120 days prior to the index event. Treatment naïve patients or patients on short term therapy were defined as having PDC of less than or equal to 30 days in the 120 days prior to the index event.

Patients were excluded from the study if they had any of the following benefit packages which indicate patients with Medicare or a limited Medicaid drug benefit: BMM, BMD, MND, MED, CWM, SMF, SMB or MED. Patients were also excluded if they had eligibility of less than 75% of combined FFS and CCO days (approximately 9 months total enrollment) in the period of time from 6 months before to 6 months after the IE.

Under the current policy, patients on benzodiazepine therapy prior to implementation of the policy were grandfathered at their current dose. However, a PA would be required for any patients who had a change in therapy or dose, and any patients on long-term therapy would be asked to either taper their dose or provide appropriate rationale for long-term treatment with a benzodiazepine. For patients on long-term therapy, the number of patients with changes in therapy including increasing dose, decreasing dose, or switching medications in the 6 months following the IE was documented. The baseline daily dose was defined as the average daily dose for benzodiazepine claims in the 120 days prior to the IE. Claims were assessed in the 6 months following the IE to determine if therapy was changed to a different benzodiazepine or patients had paid claims for a higher or lower daily dose. Patients were classified as having a change in dose if, in the 6 months following the IE, the average dose for the proportion of covered days was at least 1 mg per day higher or lower than the average dose assessed prior to the index event.

For treatment naïve patients or patients on short-term benzodiazepine therapy, ongoing therapy for increased doses or switching medications was also documented in the 6 months following the IE. The proportion of patients who transitioned to long-term treatment was estimated using average number of covered days and the proportion of days covered (PDC) in the 6 months following the IE. Current policy would allow for approximately 45 days of therapy over 6 months without PA. Short-term therapy over a period of 6 months would correspond to a PDC of up to 25% (≤45 days), intermediate therapy corresponds to PDC of 25-75% (46 to 135 days), and long-term therapy corresponds to a PDC greater than 75% (>135 days every 6 months). Short-term therapy would not require PA, whereas intermittent or long-term therapy would require PA approval. Intermittent therapy may indicate therapy of medium duration, sporadic “as needed” usage, or low adherence to continuously prescribed therapy.

Diagnoses of epilepsy was identified via medical claims indicating a diagnosis in the 2 years prior to the IE (see **Appendix 5** for diagnosis codes). In addition, patients were categorized based on diagnosis identified in 2 years prior to the IE using diagnosis codes in **Appendix 5.** Patients prescribed concomitant sedating medications including opioids, sedatives, or muscle relaxants were quantified. Concomitant therapy for sedating medications was defined as greater than 30 overlapping days’ supply following the IE with benzodiazepine and sedating mediations based on FFS or CCO pharmacy claims. Similarly, the proportion of patients with a history of claims for an antidepressant or antipsychotic medications in the 120 days prior to the IE was documented. A list of included medications is available in **Appendix 4**.

Potential benefits of the policy were assessed through evaluation of benzodiazepine or sedative poisoning or overdose. Overall rates of benzodiazepine-related poisoning, accidental poisoning, and adverse effects were identified with diagnosis codes in **Appendix 5**. Diagnoses for benzodiazepine use were evaluated in the month following a paid claim. Respiratory depression and overdose may also often occur upon concomitant use of multiple sedating medications and diagnoses used for billing may not accurately represent the specific sedating medications involved. Therefore, the rate of overdose and poisoning from any sedating medication was also evaluated. Overdose or poisoning associated with sedating medications included a broad variety of classes such as benzodiazepines, opioids (both prescription and illicit), alcohol, tricyclic antidepressants, sleep medications, barbiturates, other anesthetics, muscle relaxants, cold drugs, and respiratory depressants which were not otherwise specified.

Patients potentially paying cash for claims were identified using a proxy based on denied claims. Patients were classified as potentially paying cash if they had had at least 2 distinct denied claims occurring at least 5 days apart in the 120 days following an initial benzodiazepine denial AND within 4 days of both denied

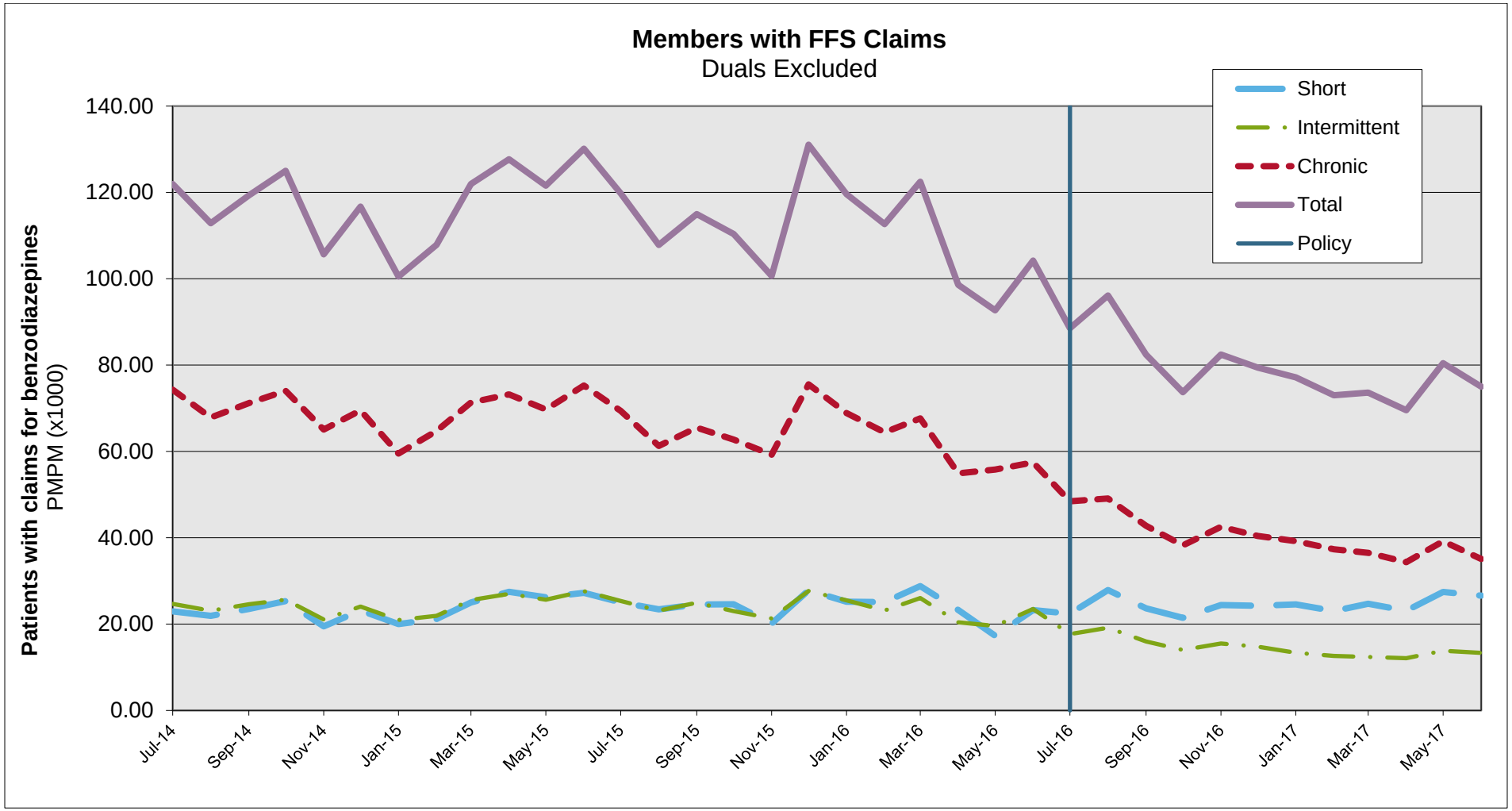
claims, did not have a paid claim for a benzodiazepine. Denied claims were counted only once if there were multiple denials for a claim with same prescription number and refill quantity.

Potential harms as a result of the policy were assessed through examination of emergency department visits, hospitalizations (**Appendix 6**), and associated diagnostic codes (**Appendix 5**). This initial analysis of harms categorized patients according to the first benzodiazepine claim in the reporting period (the IE), and subsequent paid or denied benzodiazepine claims may not be captured in the analysis. Using this method avoids counting patients multiple times, but it may also potentially miss valuable information in patients with subsequent paid or denied benzodiazepine claims. Due to these limitations with the initial analysis, a post-hoc analysis was conducted to further evaluate patients who may have had multiple medical encounters or multiple denied claims over the course of the evaluation period. All ED visits and hospitalizations for all patients in the pre-specified populations were categorized into the following groups according to the most recent paid or denied benzodiazepine claim occurring within 90 days before the encounter: 1) encounters with a paid benzodiazepine claim prior to the event, 2) encounters with a denied benzodiazepine claim prior to the event, 3) encounters without a benzodiazepine claim within 90 days before the event. If a patient had both a paid and denied claim on the same day, the encounter was categorized as paid. This analysis captures all ED visits or hospitalizations for the patients during the study period, and patients would be counted more than once if they had multiple medical visits. Subsequently, data for this analysis may be more heavily influenced by members with frequent ED visits or hospitalizations.

Results:

The proportion of members who continue to receive benzodiazepines as long-term therapy after an initial claim is shown in **Figure 1**. After implementation of the policy there was a decrease in the total number of patients with claims for a benzodiazepine and the number of patients with claims for chronic benzodiazepine use (>90 days of benzodiazepine therapy following the IE). The number of patients classified as using benzodiazepines short-term (6-30 days of benzodiazepine therapy in the 120 days following their first claim) remained unchanged following implementation of the policy.

Figure 1. Unique patient count of Medicaid members (FFS and CCO) with a FFS benzodiazepine claim in the past 3 years from 7/1/14 to 3/1/18 stratified by treatment duration. Short-term benzodiazepine use was classified as having a PDC (including both CCO and FFS claims) of 6-30 days following the IE, patients with intermittent benzodiazepine treatment were classified as having a PDC of 31-89 following the IE, and chronic use was classified as greater than 90 days of therapy following the IE.



Since implementation of the policy, the overall rate of benzodiazepine poisonings and adverse events has declined for members with a history of long-term use (**Figure 2**). This coincides with a decline observed in the number of patients prescribed long-term benzodiazepine therapy. Comparatively there was little change in the overall rate of poisoning from any sedative (**Figure 3**). It's unclear if the decline in benzodiazepine poisoning and adverse effects is entirely due to policy implementation or if it may be partially impacted by changes in the population over time. The majority of patients on long-term therapy were grandfathered prior to policy implementation. Unless these patients had a change in therapy, they would not be subject to the current policy. If a patient on long-term therapy had a change in dose or drug resulting in a denied claim, providers who submitted a PA were asked to justify necessity of continued long-term use or to develop a taper plan. In addition, after policy implementation, fewer new-start patients transitioned to long-term therapy. These combined factors may have resulted in a smaller overall population of patients on long-term treatment or changes in the population of patients which may impact overall rates of poisoning and adverse effects.

Figure 2. Overall rates of benzodiazepine poisoning, accidental poisoning, and adverse effects for patients with long-term benzodiazepine use and new start patients. Diagnosis for benzodiazepine use was evaluated in the month following a paid claim.

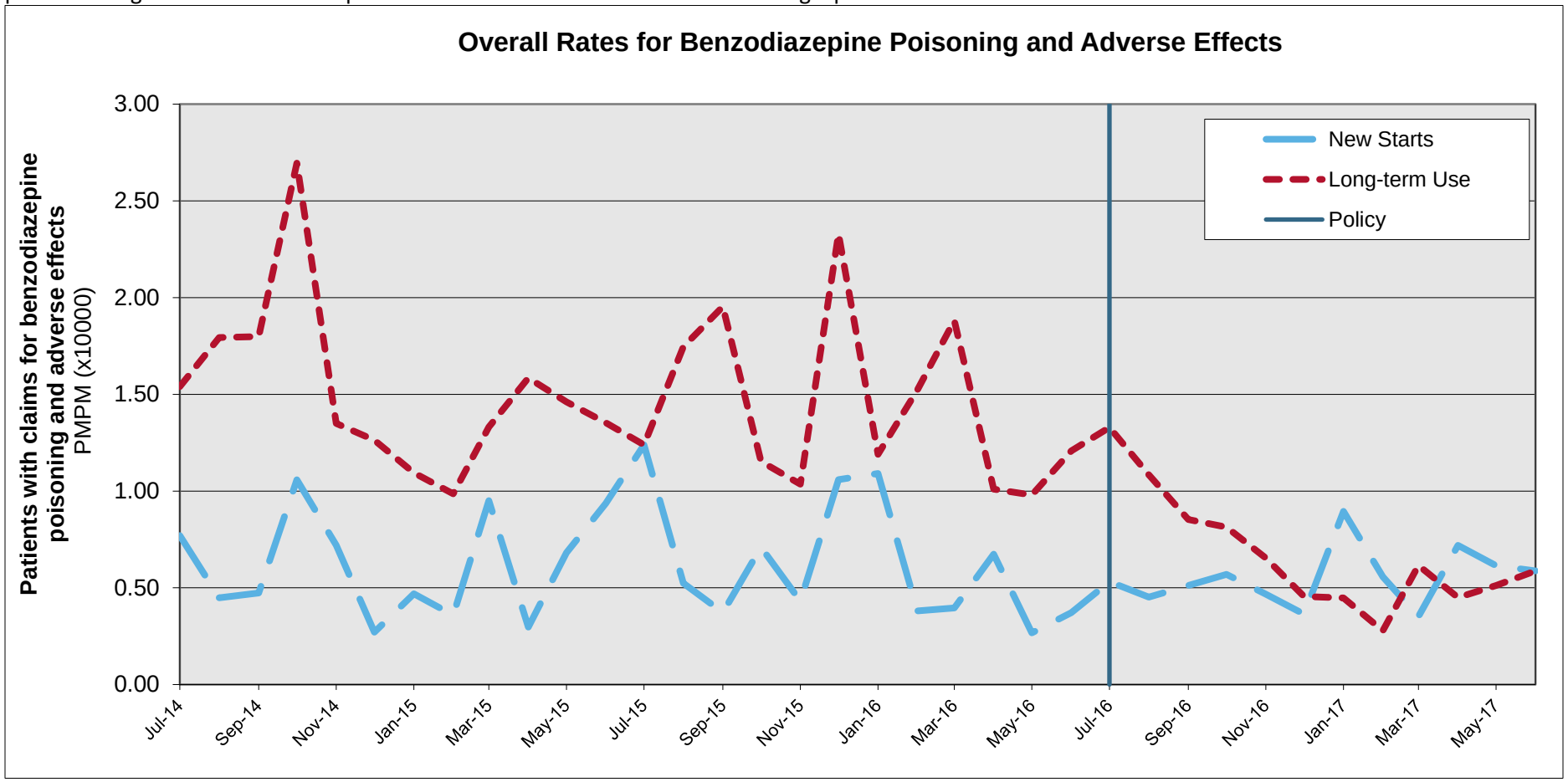
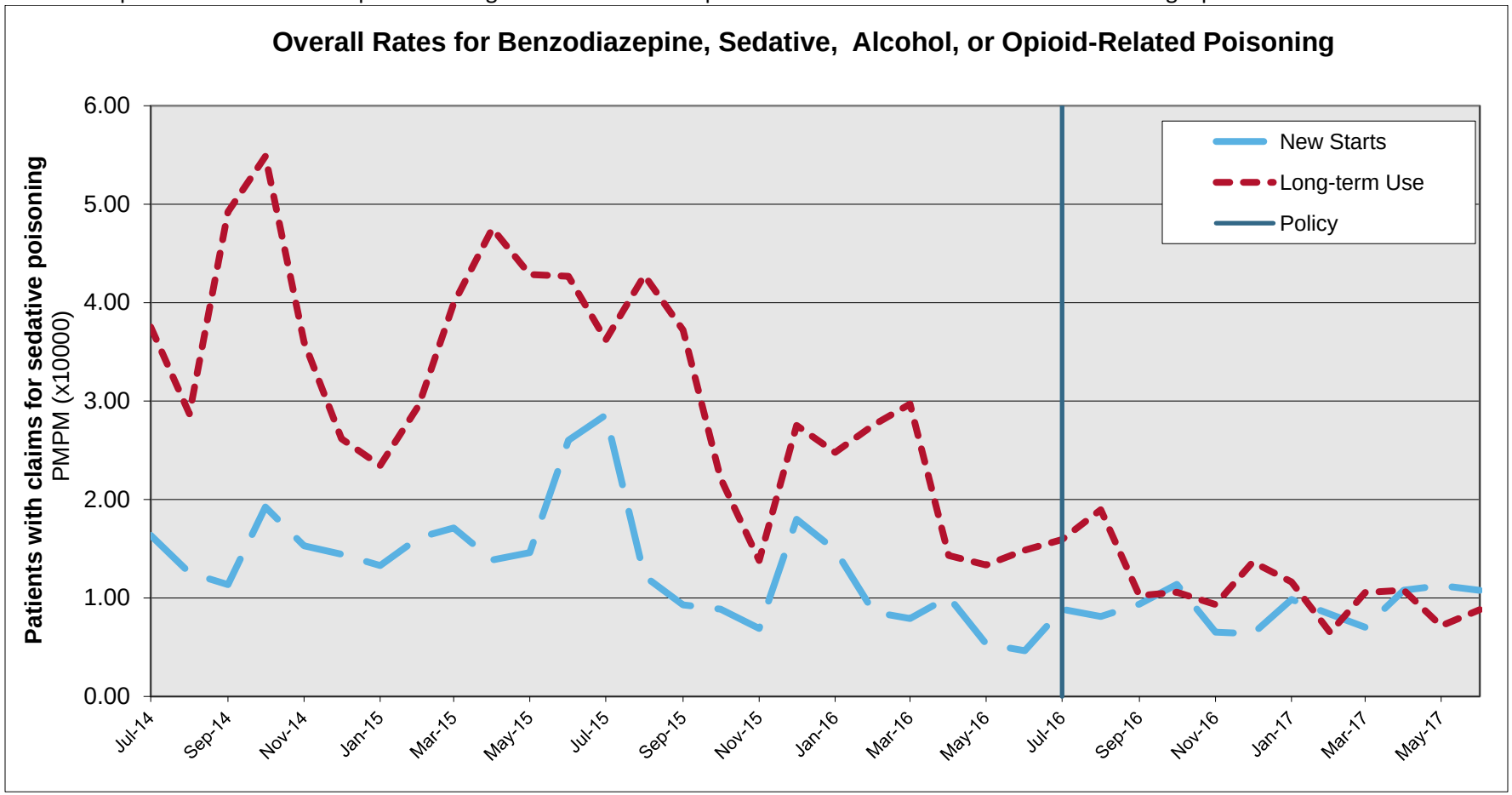


Figure 3. Overall rates of benzodiazepine, sedative, alcohol, or opioid poisoning, suicide by poisoning or accidental poisoning for patients with long-term benzodiazepine use and new-start patients. Diagnosis for benzodiazepine use was evaluated in the month following a paid claim.



Demographics for patients classified as chronic users or short-term/treatment naïve patients are shown in **Table 1**. Overall, populations were similar before and after implementation of the policy with the exception of white patients which has decreased over time. With a few exceptions discussed below, overall rates were also very similar between patients with either a paid or denied IE (data not shown). For patients with a history of long-term use (>30 days), average duration of therapy was similar after implementation of the policy for patients with continued paid claims. In patients with denied claims, average days' supply was decreased from 134 days to 88 days. This is expected given that the majority of patients with a history of benzodiazepine use were grandfathered prior to implementation of the policy. If a patient on long-term therapy had a change in dose or drug resulting in a denied claim, providers who submitted a PA were asked to justify necessity of continued long-term use or to develop a taper plan. In treatment naïve patients or patients with a history of short-term use (≤30

days), average days of coverage for was reduced from 50 days before policy implementation to 34 days after policy implementation. Current policy would allow for 30 days every 120 days or approximately 45 days every 6 months without PA.

Table 1. Baseline demographics for all IE. PDC in the 6 months following the index claim was evaluated to assess duration of therapy.

	Before		After	
N=	**31,788**		**28,149**	
New Starts and History of Short-term Use	**21,509**		**19,107**	
Mean age (range)	40	0-87	40	0-93
<13	325	1.5%	302	1.6%
13-18	688	3.2%	623	3.3%
19-60	19,145	89.0%	16,905	88.5%
>60	1,351	6.3%	1,277	6.7%
Female	15,013	69.8%	13,226	69.2%
White	6,467	30.1%	4,023	21.1%
Native American	977	4.5%	867	4.5%
Index Drug				
Alprazolam (carve-out)	6,364	29.6%	5,690	29.8%
Diazepam (carve-out)	3,883	18.1%	3,182	16.7%
Lorazepam (carve-out)	9,937	46.2%	8,869	46.4%
Clonazepam (FFS)	678	3.2%	682	3.6%
Other (carve-out)	647	3.0%	684	3.6%
Days of Coverage in 6 months after index (avg, range)	50.1	(6-185)	34.1	(0-185)
History of Long-term Use	**10,279**		**9,042**	
Mean age (range)	45	0-91	45	1-92
<13	72	0.7%	73	0.8%
13-18	155	1.5%	129	1.4%
19-60	9,059	88.1%	7,976	88.2%
>60	993	9.7%	864	9.6%
Female	7,124	69.3%	6,202	68.6%
White	4,722	45.9%	3,512	38.8%
Native American	460	4.5%	439	4.9%

Index Drug				
Alprazolam (carve-out)	3,656	35.6%	3,107	34.4%
Diazepam (carve-out)	1,806	17.6%	1,544	17.1%
Lorazepam (carve-out)	3,870	37.6%	3,413	37.7%
Clonazepam (FFS)	707	6.9%	756	8.4%
Other (carve-out)	240	2.3%	222	2.5%
Days of Coverage in 6 months after index (avg, range)	134.2	(6-185)	128.4	(0-185)

The number of patients who continued to receive long-term therapy after implementation of the policy is described in **Table 2**. Duration of therapy is estimated using days of coverage and PDC in the 6 months following the IE. Current policy would allow a patient to fill approximately 45 days every 6 months (or up to 25% PDC) without PA. Since implementation of the policy, the number of treatment naïve patients who transition to long-term therapy has decreased. Patients on continuous benzodiazepine therapy (represented by PDC >75%) decreased from 8.7% to 2.6% and patients with PDC of 26-75% decreased from 28% to 19% after policy implementation. The average days of coverage also decreased from 50 days to 34 days after implementation of the policy in patients with a history of short-term use. In patients with a history of long-term use, days of coverage were similar before and after policy implementation, though there was a slight decrease in the number of patients receiving continuous benzodiazepine therapy for more than 75% of days in the 6 months following the first claim in the reporting period (from 58.7% to 54.5%).

Table 2. Total number of patients continuing to receive long-term or short-term benzodiazepine therapy after the index event.

	Before		**After**	
All patients with a paid or denied claim	**31,788**		**28,149**	
Patients with >30 days coverage in 120 days following the IE	17,924	56.4%	11,701	41.6%
Patients with <=30 days coverage in 120 days following the IE	13,864	43.6%	16,448	58.4%
New starts and short-term use (history of use <=30 days prior to the IE)	**21,509**		**19,107**	
Days of Coverage in 6 mo. after IE (average, range)	50	6-185	34	0-185
PDC <= 25%	13,514	62.8%	14,883	77.9%
PDC 26%-75%	6,026	28.0%	3,627	19.0%
PDC > 75%	1,875	8.7%	496	2.6%
History of Long-term Use (history of use >30 days prior to the IE)	**10,279**		**9,042**	
Days of Coverage in 6 mo. after IE (average, range)	134	6-185	128	0-185
PDC <= 25%	827	8.0%	963	10.7%
PDC 26%-75%	3,393	33.0%	3,126	34.6%
PDC > 75%	6,038	58.7%	4,927	54.5%

Table 3 details the number of patients with a change in drug therapy or baseline dose (estimated as the average dose in the 120 days prior to the IE). PA is required under current policy for any patients with a history of long-term use and a change in their benzodiazepine therapy (despite grandfathering prior to policy implementation). Changes in therapy which would result in PA include changing the strength of prescribed medication (either increasing or decreasing the dose) or changing to a different benzodiazepine. In patients with a history of long-term use, approximately 74-77% were maintained on their current therapy and 23-26% of patients had a change in benzodiazepine drug or dose based on claims history. Overall, approximately 9% of patients (new starts and long-term benzodiazepine users) had a denied IE after implementation of the policy. In patients with a history of long-term use, denied claims were most common for patients with changes in therapy and accounted for approximately 70% of denied IE compared to patients without significant changes in therapy (31% of patients with a denied IE).

Table 3. Proportion of patients with a change in therapy or dose. Population represents all index events.

	Before		After	
N=	**31,788**		**28,149**	
New Starts and Short-term Use	**21,509**		**19,107**	
No change in drug or dose	10,432	48.5%	10,006	52.4%
Higher average daily dose	10,323	48.0%	8,514	44.6%
Any change in drug	1,654	7.7%	1,077	5.6%
History of Long-term Use	**10,279**		**9,042**	
No change in drug or dose	7,580	73.7%	6,953	76.9%
Patients with a change in dose	1,624	15.8%	1,142	12.6%
Lower average daily dose	762	7.4%	597	6.6%
Higher average daily dose	862	8.4%	545	6.0%
Any change in Drug	1,648	16.0%	1,268	14.0%

Table 4 shows the top 10 types of providers who most commonly prescribe benzodiazepines. Upon comparison of patients with either a paid or denied IE, rates were similar between groups (data not shown) with differences ranging from 0-4% for new start patients and 0-6% for patients on long-term therapy. The most common prescribers who initiate benzodiazepine therapy in treatment naïve patients or patients with a history of short-term use are family practitioners (24%), internists (12%), physician assistants (12%) and family nurse practitioners (11%). After implementation of the policy, duration of therapy prescribed from all providers initiating therapy in treatment naïve patients (with the exception of emergency care providers) decreased by an average of 11 to 30 days. Prior to initiation of the policy, the average number of days covered was 42 to 73 days for the top 5 prescriber types. After the policy implementation, average duration had decreased to 30-45 days. The average days of benzodiazepine therapy was longer for patients whose therapy was initiated by a specialist including psychiatrists, psychiatric mental health nurse practitioners, and neurologists (average 44 to 46 days after policy implementation).

For patients with a history of long-term benzodiazepine use, therapy was most commonly prescribed by family practitioners (24-26%), internists (14%), psychiatrists (10%), psychiatric mental health nurse practitioners (10%), and family nurse practitioners (9%). Treatment duration was relatively unchanged after implementation of the policy (115-145 days of coverage), which is expected given the majority of patients on long-term therapy would have been grandfathered on their current therapy prior to implementation of the policy.

Table 4. Number and duration of use for patients stratified by primary provider taxonomy for providers who most commonly prescribe benzodiazepines (top 10 prescriber types). Population represents all index events.

		Before			After		
		Paid Index Events		Days of Coverage in 6 months after IE	All Index Events		Days of Coverage in 6 months after IE
	N=	31,788			28,149		
New Starts and Short-term Use		**21,509**	**%**	**Avg**	**19,107**	**%**	**Avg**
1	Family Practitioner	5,302	24.7%	50.0	4,536	23.7%	34.0
2	Internist	2,603	12.1%	49.6	2,276	11.9%	34.3
3	Physician Assistants	2,514	11.7%	42.4	2,313	12.1%	30.0
4	Family Nurse Practitioner	2,293	10.7%	51.6	2,090	10.9%	33.5
5	Psychiatrist	1,273	5.9%	72.9	1,153	6.0%	45.5
9	Emergency Med Practitioner	1,044	4.9%	20.0	762	4.0%	17.4
7	Nurse Practitioner (default Spec)	925	4.3%	57.6	905	4.7%	38.5
6	Psychiatric Mental Health Nurse Practitioner	907	4.2%	76.2	936	4.9%	46.2
8	Advance Practice Nurse	774	3.6%	57.3	604	3.2%	39.2
10	Neurologist	352	1.6%	55.2	311	1.6%	44.2
History of Long-term Use		**10,279**	**%**	**Avg**	**9,042**	**%**	**Avg**
1	Family Practitioner	2,703	26.3%	133.0	2,219	24.5%	127.2
2	Internist	1,458	14.2%	134.2	1,208	13.4%	133.0
3	Psychiatrist	1,072	10.4%	139.7	975	10.8%	132.5
4	Psychiatric Mental Health Nurse Practitioner	1,009	9.8%	142.1	894	9.9%	133.5
5	Family Nurse Practitioner	890	8.7%	127.2	833	9.2%	121.6
6	Physician Assistants	689	6.7%	127.3	664	7.3%	121.0
7	Nurse Practitioner (default Spec)	492	4.8%	133.4	523	5.8%	128.9
8	Advance Practice Nurse	484	4.7%	139.5	414	4.6%	130.0
9	Neurologist	220	2.1%	147.8	213	2.4%	145.4
10	Emergency Med Practitioner	90	0.9%	126.1	96	1.1%	115.4

Table 5 describes common diagnoses of interest in patients prescribed benzodiazepines. In patients with a history of short-term benzodiazepine use, approximately 85% of the population had OHP-funded mental health diagnoses, 6% had indications for unfunded diagnoses without any documented funded diagnosis, and 10% had no documented indication for benzodiazepine treatment. Over 60% of treatment naïve patients prescribed benzodiazepines had anxiety

disorders, 47-49% of patients had depression or another mood disorder, and 13-15% had panic disorder. Rates for subgroups of patients with paid or denied IE followed similar trends with only small differences between patients with a paid IE and those with a denied IE (data not shown). Of interest, approximately 19-21% of patients had a diagnoses of PTSD or acute stress disorders and 20% of the population had diagnoses indicating a history of substance abuse. Current guidelines recommend against the use of benzodiazepines (as monotherapy or combination therapy) for treatment of PTSD due to limited evidence of efficacy and know risks associated with treatment.[2] However, in patients with multiple diagnoses, it is unclear what specific diagnosis may be related to benzodiazepine treatment based on analyses of claims data. In addition, diagnoses based on claims data may be incomplete.

Similar trends were observed in patients with a history of long-term benzodiazepine use. The most common diagnoses included anxiety (68-71%), depression/mood disorders (54-56%), PTSD/acute stress disorders (27-28%), bipolar disorder (20%), and panic disorder (16-18%). Diagnoses for substance abuse were present in 19-25% of the population and approximately 3-5% of patients had no documented indication for benzodiazepine treatment. Of the patients with a denied index event after implementation of the policy, more patients had a diagnosis of depression or mood disorder (65%), PTSD or acute stress disorder (40%), bipolar disorder (30%), or substance abuse disorder (36%) compared to the overall population or patients with a paid IE (56%, 28%, 19%, and 25% respectively). The overall proportion of patients with a paid or denied IE was similar for patients with other diagnoses.

Table 5. Benzodiazepine utilization stratified by diagnoses of interest identified in the 2 years prior to the index event. Patients may have more than one funded diagnosis. Patients are listed with other conditions only if they do not have another funded diagnosis.

	Before			After		
	Paid Index Events		Days of Coverage in 6 months after IE	All Index Events		Days of Coverage in 6 months after IE
N=	31,788			28,149		
New Starts and Short-term Use	**21,509**	%	**Avg**	**19,107**	%	**Avg**
Funded conditions	18,166	84.5%	50.9	16,669	87.2%	34.6
Anxiety disorders	13,291	61.8%	51.4	12,625	66.1%	34.9
Depression or other mood disorder	10,119	47.0%	53.2	9,413	49.3%	35.4
Substance Abuse	4,448	20.7%	50.6	4,632	24.2%	33.1
PTSD or acute stress disorder	4,026	18.7%	58.2	4,062	21.3%	37.5
Panic disorder	2,871	13.3%	52.2	2,858	15.0%	35.7
Bipolar disorder	2,550	11.9%	62.5	2,375	12.4%	40.1
Malignant Neoplasm or other end of life diagnosis	2,358	11.0%	49.1	1,846	9.7%	35.9
Epilepsy	1,226	5.7%	51.5	1,469	7.7%	35.5
Schizophrenic disorders	761	3.5%	68.6	792	4.1%	43.1
Other conditions	1,384	6.4%	43.7	1,115	5.8%	29.1
Back and spine conditions (funded)	1,072	5.0%	41.9	884	4.6%	27.5
Fibromyalgia and chronic pain (unfunded)	431	2.0%	48.3	364	1.9%	32.0
Insomnia (unfunded)	344	1.6%	50.4	308	1.6%	30.8

None of the Above	1,959	9.1%	47.5	1,323	6.9%	32.6
History of Long Term Use	**10,279**	%	**Avg**	**9,042**	%	**Avg**
Funded conditions	9,260	90.1%	134.4	8,404	92.9%	128.2
Anxiety disorders	6,985	68.0%	133.1	6,558	72.5%	126.5
Depression or other mood disorder	5,577	54.3%	132.7	5,161	57.1%	126.6
PTSD or acute stress disorder	2,734	26.6%	135.0	2,613	28.9%	125.9
Bipolar disorder	2,017	19.6%	136.7	1,846	20.4%	127.7
Substance Abuse	1,980	19.3%	133.4	2,379	26.3%	124.7
Panic disorder	1,677	16.3%	133.7	1,671	18.5%	127.2
Malignant Neoplasm or other end of life diagnosis	1,297	12.6%	133.2	910	10.1%	127.4
Schizophrenic disorders	809	7.9%	147.2	811	9.0%	137.7
Epilepsy	790	7.7%	143.4	884	9.8%	136.0
Other conditions	472	4.6%	133.3	350	3.9%	133.6
Back and spine conditions (funded)	324	3.2%	130.8	267	3.0%	133.3
Fibromyalgia and chronic pain (unfunded)	220	2.1%	131.9	150	1.7%	141.5
Insomnia (unfunded)	139	1.4%	132.3	106	1.2%	127.1
None of the Above	547	5.3%	132	288	3.2%	128.7

Medications of interest for mental health conditions are shown in **Table 6** and are generally consistent with diagnoses observed in **Table 5**. Patients without a history of chronic benzodiazepine use commonly had at least one recent claim for an SSRI, SNRI, or other antidepressant (such as bupropion, trazodone or buspirone). Approximately 12% of treatment naïve patients or patients with a history of short-term benzodiazepine use had recent claims for an antipsychotic. In patients with a history of long-term use, utilization of SSRIs or SNRIs (50%), other antidepressants (29%), and second generation antipsychotics (23-24%) was slightly more frequent than patients who were treatment naïve. Overall, utilization for mental health drugs was similar before and after implementation of the policy.

In patients with a history of long-term use, concomitant use of sedating medications including muscle relaxants and opioids occurred in 9-10% and 17-19% of the population, respectively. There was overall little difference before versus after implementation of the policy.

With a few exceptions, trends were similar in patients with a paid IE versus patients with a denied IE. In new start patients, denied IE was slightly more common for patients with claims for SSRI/SNRIs and second generation antipsychotics (difference of 6% compared to the percent of patients with paid IE). Similar patterns were observed in patients on long-term therapy: patients with claims for SSRIs/SRNIs (56%), other antianxiety medications (37%), and second generation antipsychotics (33%) more commonly had denied IE compared to the proportion of patients with a paid IE (50%, 28%, and 23% respectively). Data is likely influenced partially by disease and symptom severity. Patients are more likely to request long-term benzodiazepine therapy or have changes in their

current therapy (and have a subsequent denied claim) if they have severe or continual symptoms. Patients are also more likely to be on other mental health therapy if they have more severe or continual symptoms.

Table 6. Benzodiazepine utilization stratified by concurrent medications. See **Appendix 4** for a list of medications included in each category.

	Before			After		
	Paid IE		Days of Coverage in 6 months after IE	All IE		Days of Coverage in 6 months after IE
N=	31,788			28,149		
New Starts and Short-term Use	**21,509**	%	**Avg**	**19,107**	%	**Avg**
Sedating medications (Concurrent)						
Muscle relaxants	456	2.1%	107.2	268	1.4%	74.1
Opioid (short- or long-acting)	851	4.0%	107.1	405	2.1%	74.3
Sedatives	130	0.6%	117.0	74	0.4%	80.3
Antidepressants/antianxiety (120 days prior)						
SSRI/SNRI	9,236	42.9%	54.1	8,125	42.5%	36.2
TCA	1,359	6.3%	57.5	1,137	6.0%	38.8
MAOI	4	0.0%	25.0	2	0.0%	12.5
Other	4,719	21.9%	57.5	4,319	22.6%	37.0
Antipsychotics (120 days prior)						
First generation	243	1.1%	66.5	211	1.1%	41.9
Second generation	2,368	11.0%	67.3	2,292	12.0%	42.0
Parenteral	72	0.3%	79.0	137	0.7%	48.0
History of Long-term Use	**10,279**	%	**Avg**	**9,042**	%	**Avg**
Sedating medications (Concurrent)						
Muscle relaxants	962	9.4%	155.3	839	9.3%	152.2
Opioid (short- or long-acting)	2,038	19.8%	153.9	1472	16.3%	150.9
Sedatives	235	2.3%	154.0	204	2.3%	148.7
Antidepressants/antianxiety (120 days prior)						
SSRI/SNRI	5,187	50.5%	132.5	4591	50.8%	126.6
TCA	1,069	10.4%	134.8	890	9.8%	131.2
MAOI	4	0.0%	127.8	4	0.0%	111.3
Other	3,009	29.3%	134.1	2607	28.8%	126.2

Antipsychotics (120 days prior)						
First generation	283	2.8%	148.0	253	2.8%	146.8
Second generation	2,345	22.8%	139.8	2182	24.1%	133.1
Parenteral	67	0.7%	155.6	23	0.3%	134.2

Disposition of denied claims is shown in **Table 7**. Of the patients with a denied benzodiazepine claim, approximately 69% of treatment naïve patients and 77% of patients with a history of long-term use had a subsequent paid claim within 90 days. The vast majority of patients without further benzodiazepine therapy did not have a PA request and a significant number (20% of new starts and 44% of long-term benzodiazepine users) had a pattern of denied claims which may indicate they paid cash for their prescriptions.

Table 7. Disposition of denied pharmacy claims after implementation of the policy. Subsequent benzodiazepine claims were classified as either FFS pharmacy claims or CCO encounter claims for a benzodiazepine.

	New Starts and Short Term Use		**History of Long Term Use**	
	N	%	N	%
Index Event Denied Claim	1,658		858	
Benzodiazepine claim filled within 30 days	914	55.1%	495	57.7%
Benzodiazepine claim filled within 90 days	235	14.2%	168	19.6%
Never had a benzodiazepine claim within 90 days of a denied claim	509	30.7%	195	22.7%
PA not requested in the 5 days before or 30 days after the denied claim	495	97.2%	192	98.5%
PA denied in the 5 days before or 30 days after the initial denied claim	0	0.0%	0	0.0%
Never received drug and had diagnosis of epilepsy, malignant neoplasm or end of life diagnosis	11	2.2%	2	1.0%
Number of patients potentially paying cash	104	20.4%	85	43.6%

Table 8 compares the incidence of hospitalization and emergency department visits for patients with paid or denied claims for benzodiazepines before and after the policy. Diagnoses of interest included sedative poisoning, suicide or intentional self-harm, epilepsy, malignant neoplasm or other end of life diagnoses, and mental health disorders. In treatment naïve patients, there was no change overall rates for hospitalizations or ED visits before and after implementation of the policy (4-5% and 22-23% respectively). In patients with a history of long-term benzodiazepine use, overall rates of hospitalization and ED visits were also similar before and after the policy (2% and 12%, respectively).

Table 9 examines the number of ED visits or hospitalizations for all members over the course of the entire study period. Medical visits were categorized by the presence or absence of the most recent benzodiazepine claim prior to the event. For the entire population, only 7.2% of hospitalizations and 8.8% of ED visits occurred following a denied benzodiazepine claim. In new start patients and patients with a history of short-term use, hospitalizations and ED visits commonly occurred following a paid benzodiazepine claim (29.7% and 38.3%, respectively) and greater than 50% of events were not temporally related to any benzodiazepine claims prior to the encounter. In this population, less than 10% of ED visits and hospitalizations occurred following a denied benzodiazepine

claim. In patients with a history of long-term use, approximately 80% of ED visits and hospitalizations occurred following a paid benzodiazepine claim. Only a small proportion of ED visits (6%) and hospitalizations (6%) occurred following a denied benzodiazepine claim.

Table 8. Assessment of potential unintended harms and safety signals after implementation of the policy. Harms were defined as events (including hospitalizations, emergency department visits, or death) within 3 months following the IE for patients after implementation of the policy compared to overall rates of hospitalization and emergency department visits before implementation of the policy.

	Before		After	
	Paid Index Events		All Index Events	
N=	31,788		28,149	
New Starts and Short-term Use	**21,509**	%	**19,107**	%
Any Hospitalization	967	4.5%	929	4.9%
Any Emergency Department (ED) Visit	4758	22.1%	4436	23.2%
Death	32	0.1%	14	0.1%
Composite including patients with any of the following (patients counted only once):	132	0.6%	170	0.9%
– Hospitalization or ED visit associated with diagnosis of benzodiazepine, sedative, alcohol, or opioid related poisonings, suicide by poisoning, or accidental poisoning	128	0.6%	160	0.8%
– Medical claims for naloxone administration	7	0.0%	14	0.1%
Composite including patients with any of the following (patients counted only once):	983	4.6%	943	4.9%
– Hospitalization or ED visit associated with diagnosis of suicide, intentional or undetermined poisoning, or other intentional self-harm	81	0.4%	78	0.4%
– Hospitalization or ED visit associated with diagnosis of epilepsy, malignant neoplasm or end of life diagnosis	293	1.4%	314	1.6%
– Hospitalization or ED visit associated with a psychiatric diagnosis (bipolar disorder, PTSD or acute stress disorders, depression or mood disorder, schizophrenic disorders, panic disorders, anxiety disorders)	687	3.2%	632	3.3%
History of Long-term Use	10,279	%	9,042	%
Any Hospitalization	221	2.2%	186	2.1%
Any Emergency Department (ED) Visit	1291	12.6%	1112	12.3%
Death	10	0.1%	9	0.1%
Composite including patients with any of the following (patients counted only once):	32	0.3%	48	0.5%
– Hospitalization or ED visit associated with diagnosis of benzodiazepine, sedative, alcohol, or opioid related poisonings, suicide by poisoning, or accidental poisoning	32	0.3%	47	0.5%
– Medical claims for naloxone administration	1	0.0%	1	0.0%

Composite including patients with any of the following (patients counted only once):	201	2.0%	212	2.3%
– Hospitalization or ED visit associated with diagnosis of suicide, intentional or undetermined poisoning, or other intentional self-harm	25	0.2%	25	0.3%
– Hospitalization or ED visit associated with diagnosis of epilepsy, malignant neoplasm or end of life diagnosis	42	0.4%	55	0.6%
– Hospitalization or ED visit associated with a psychiatric diagnosis (bipolar disorder, PTSD or acute stress disorders, depression or mood disorder, schizophrenic disorders, panic disorders, anxiety disorders)	152	1.5%	153	1.7%

Table 9. Count of ED visits and hospitalizations during evaluation periods, by presence or absence of a paid or denied benzodiazepine claim in 90 days prior to the event. Patients with more than one ED visit or hospitalization will be counted more than once.

	Before				After			
	Hospitalizations		ED Visits		Hospitalizations		ED Visits	
All Visits	**5,557**		**17,478**		**4,961**		**15,226**	
Denied benzo claim before the event					357	7.2%	1,334	8.8%
Paid benzo claim before the event	2,995	53.9%	10,497	60.1%	2,157	43.5%	7,711	50.6%
No benzo claim (paid or denied) within 90 days before the event	2,562	46.1%	6,981	39.9%	2,447	49.3%	6,181	40.6%
All Visits for New Starts and Short-term Use patients	**3,964**		**12,096**		**3,628**		**10,667**	
Denied benzo claim before the event					273	7.5%	1,053	9.9%
Paid benzo claim before the event	1,606	40.5%	5,934	49.1%	1,077	29.7%	4,084	38.3%
No benzo claim (paid or denied) within 90 days before the event	2,358	59.5%	6,162	50.9%	2,278	62.8%	5,530	51.8%
All Visits for Long-Term Use patients	**1,593**		**5,382**		**1,333**		**4,559**	
Denied benzo claim before the event					84	6.3%	281	6.2%
Paid benzo claim before the event	1,389	87.2%	4,563	84.8%	1,080	81.0%	3,627	79.6%
No benzo claim (paid or denied) within 90 days before the event	204	12.8%	819	15.2%	169	12.7%	651	14.3%

Limitations:

Several limitations exist as a result of the retrospective nature of this analysis. First, data is based on claims history which may not accurately reflect true patient diagnoses or correlate with actual medication adherence. Both ICD-9 and ICD-10 diagnosis codes were used to identify diagnoses for patients. Though efforts were made to accurately identify comparable codes, there may be differences in diagnoses based on the ICD version for claims identified before and after October 2015 when the ICD-10 version was implemented. In addition, use of proportion of days covered attempts to estimate the frequency which a patient takes a prescription, but accuracy of this method has not been validated and patients may not always be categorized appropriately. For example, a patient with PDC less than 25% over 6 months (defined as short-term therapy) could have up to 45 days of continuous benzodiazepine coverage in the reporting period which could be indicative of long-term therapy initiation. Provider specialization was identified using the National Provider Identifier (NPI) number and the associated

primary provider taxonomy which may also be inaccurate, out-of-date, or incomplete for some providers. Prescribers with multiple specialties or designations may not be identified.

The retrospective nature of the study also does not control for potential unknown confounders which may influence results of the analysis. Potential confounders include changes in the population over time or changes in the general prescribing patterns of providers. For example, data on poisoning and overdose of benzodiazepines or sedatives may be influenced by other statewide initiatives involving opioid prescribing. Similarly, emergency department visits and hospitalizations may be influenced by a variety of factors. Patients with more severe illness or less stable disease are more likely to have denied claims due to changes in therapy and are also likely to visit the ED more frequently. However, overall rate of ED visits and hospitalizations was unchanged over time, and analysis of ED visits and hospitalizations demonstrated that only a small proportion of overall events occurred following a denial for a benzodiazepine.

Another confounding factor may be stability of primary care for the member. Typically upon receipt of a denied claim, the pharmacy will notify the provider that a PA is required, and the provider will submit a PA request if appropriate. However, for almost 23% of patients with a denied claim, a prior authorization request was never submitted from the provider. It's unclear why a PA was never requested for these patients. These patients may have paid cash for the prescription, or if they were transitioning between providers, the PA request may not have reached the correct provider. Because data reflect only claims paid via Medicaid, claims which may be paid with cash or through primary insurance are not captured. Though surrogate estimates based on denied claims indicate some patients may be paying cash for their prescriptions, the method used may not accurately identify people paying cash. The exact percentage of patients who paid cash is unclear.

References:

1. McDonagh M, Crabtree E, Stoner R. Benzodiazepines. Final Summary Review prepared by the Pacific Northwest Evidence-based Practice Center for the Drug Effectiveness Review Project. Oregon Health & Science University, Portland, Oregon. Available with membership in the Drug Effectiveness Review Project. 2017.
2. Management of Posttraumatic Stress Disorder Work Group. VA/DoD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder. Version 3.0. Washington, DC: Veterans Health Administration and Department of Defense. 2017.
3. Food and Drug Administration. Medical Product Safety Information. http://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/ Accessed July 13, 2018.

Benzodiazepines

Goal(s):

- Approve only for OHP-funded diagnoses.
- Prevent inappropriate long-term benzodiazepine use beyond 4 weeks for new starts (no history within the last 120 days).
- Approve long-term use only for indications supported by the medical literature.

Length of Authorization:

- 6 months to 12 months (criteria-specific)

Requires PA:

- All benzodiazepines used beyond 4 weeks. Short-term use does not require PA.

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have a malignant neoplasm or other end-of-life diagnosis (ICD10 C00.xx-D49.xx or Z51.5)?	**Yes:** Approve for 12 months	**No:** Go to #3

Approval Criteria		
3. Is the diagnosis an OHP-funded diagnosis?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
~~3.~~4. Does the patient have a seizure disorder diagnosis? ~~(ICD10 G40.xx; F44.5; R56.9; G93.81; R56.1; R56.9; G93.81; G83.8; P90)?~~	**Yes:** Approve for 12 months	**No:** Go to #5
~~Is the diagnosis an OHP-funded diagnosis?~~	~~**Yes:** Go to #5~~	~~**No:** Pass to RPh. Deny; not funded by the OHP.~~
5. Is the request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #6
6. Is the request for treatment of post-traumatic stress disorder (PTSD)? Note: Risks of benzodiazepine treatment outweigh benefits for patients with PTSD. Treatment with benzodiazepines is not recommended.	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #7
7. Is the request for treatment of anxiety or panic disorder?	**Yes:** Go to #8	**No:** Go to #9

Approval Criteria		
~~4.~~8. Is the medication prescribed by or in consultation with a psychiatrist OR does the patient have a documented trial and failure, contraindication, intolerance, or inability to access recommended first-line treatment options including antidepressants AND psychotherapy (e.g. behavioral therapy, relaxation response training, mindfulness meditation training, eye movement desensitization and reprocessing)? Note: An adequate trial to determine efficacy of an SSRI or SNRI is 4-6 weeks.	**Yes:** Go to #11 Document trial, contraindication, or intolerance to treatment options.	**No:** Pass to RPh; Deny; medical appropriateness. Recommend adequate trial of first-line therapies. If provider requests short-term approval with a plan to start additional therapy, approval may be granted for up to 3 months. Subsequent requests must document experience with first-line treatment options.
9. Is the request for treatment of psychosis, schizophrenia or schizoaffective disorder?	**Yes:** Go to #10	**No:** Go to #11
10. Is the medication prescribed by or in consultation with a psychiatrist OR does the patient have an adequate trial and failure, contraindication, intolerance, or inability to access recommended first-line treatment options including second-generation antipsychotics AND psychotherapy (e.g. counseling, cognitive behavioral therapy, social skills training, or psychoeducation)? Note: For continued symptoms, assess adherence and dose optimization. For patients on an adequate dose of antipsychotic, guidelines recommend trial of a second antipsychotic or augmentation with a mood stabilizer.	**Yes:** Go to #11 Document trial, contraindication, or intolerance to treatment options.	**No:** Pass to RPh; Deny; medical appropriateness. Recommend adequate trial of first-line therapies. If provider requests short-term approval with a plan to start additional therapy, approval may be granted for up to 3 months. Subsequent requests must document experience with first-line treatment options.
~~5.~~11. Is the patient on a concurrent sedative, hypnotic, muscle relaxant, or opioid?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #12

Approval Criteria		
~~6.~~12. RPh only: Is there appropriate rationale to support long-term benzodiazepine use for this indication? For anxiety, panic disorder, or schizophrenia, provider rationale should include information from relevant chart notes. For other diagnoses, provider must document supporting medical literature.	**Yes:** Approve for up to 6 months.	**No:** Deny; medical appropriateness.

Renewal Criteria		
1. Is the request for a decrease in daily dose OR a change in drug with the intent to taper the dose?	**Yes:** Approve for up to 6 months or length of taper, whichever is less.	**No:** Go to #2
2. Is the request for an increase in dose?	**Yes:** Go to #3	**No:** Go to #4
3. Has the patient failed all clinically appropriate first-line adjunct treatment options OR, when applicable, is the patient adherent to recommended first-line treatment options for their condition?	**Yes:** Go to #4	**No:** Pass to RPh; Deny; medical appropriateness. Recommend trial of alternative therapies. If provider requests short-term approval with a plan to start additional therapy, approval may be granted for up to 3 months. Subsequent requests must document experience with first-line treatment options.

Renewal Criteria		
4. Is there documentation based on medical records that provider and patient have discussed whether benefits of long-term therapy (e.g. symptom improvement, social function, number of hospitalizations, etc) continue to outweigh risks of therapy (e.g. sedation, dependence, cognitive dysfunction and/or psychiatric instability)?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh; Deny; medical appropriateness. Recommend trial of gradual taper plan. Approval may be granted for up to 3 months to allow time to develop a taper plan. Subsequent requests must document progress toward taper.

P&T Review: *91/18(SS), 3/14*
Implementation: *TBD; 5/1/16*

Appendix 2:

Table A1. Benzodiazepines codes, PDL, and carve-out status

HSN	GSN	Drug Strength	Generic	PDL	Carveout
001617	003773	0.25 mg	ALPRAZOLAM		Y
001617	058847	0.25 mg	ALPRAZOLAM		Y
001617	003774	0.5 mg	ALPRAZOLAM		Y
001617	050399	0.5 mg	ALPRAZOLAM		Y
001617	058848	0.5 mg	ALPRAZOLAM		Y
001617	003775	1 mg	ALPRAZOLAM		Y
001617	050400	1 mg	ALPRAZOLAM		Y
001617	058849	1 mg	ALPRAZOLAM		Y
001617	021523	1 mg/mL	ALPRAZOLAM		Y
001617	015566	2 mg	ALPRAZOLAM		Y
001617	050401	2 mg	ALPRAZOLAM		Y
001617	058850	2 mg	ALPRAZOLAM		Y
001617	052143	3 mg	ALPRAZOLAM		Y
001656	046191	12.5 mg-5 mg	AMITRIPTYLINE/CHLORDIAZEPOXIDE		Y
001656	046192	25 mg-10 mg	AMITRIPTYLINE/CHLORDIAZEPOXIDE		Y
001611	003739	25 mg	CHLORDIAZEPOXIDE		Y
001610	003734	10 mg	CHLORDIAZEPOXIDE HCL		Y
001610	003735	25 mg	CHLORDIAZEPOXIDE HCL		Y
001610	003736	5 mg	CHLORDIAZEPOXIDE HCL		Y
002037	004902	5 mg-2.5 mg	CHLORDIAZEPOXIDE/CLIDINIUM BR		
001894	051983	0.125 mg	CLONAZEPAM	N	
001894	051984	0.25 mg	CLONAZEPAM	N	
001894	004560	0.5 mg	CLONAZEPAM	Y	
001894	051985	0.5 mg	CLONAZEPAM	N	
001894	004561	1 mg	CLONAZEPAM	Y	
001894	051986	1 mg	CLONAZEPAM	N	
001894	004562	2 mg	CLONAZEPAM	Y	
001894	051987	2 mg	CLONAZEPAM	N	
001612	003744	15 mg	CLORAZEPATE DIPOTASSIUM		Y
001612	003745	3.75 mg	CLORAZEPATE DIPOTASSIUM		Y
001612	003746	7.5 mg	CLORAZEPATE DIPOTASSIUM		Y
001615	003766	10 mg	DIAZEPAM		Y
001615	003767	2 mg	DIAZEPAM		Y
001615	003768	5 mg	DIAZEPAM		Y
001615	003764	5 mg/5 mL (1 mg/mL)	DIAZEPAM		Y

001615	068715	5 mg/5 mL (1 mg/mL, 5 mL)	DIAZEPAM	N	Y
001615	003765	5 mg/mL	DIAZEPAM		Y
004846	003757	0.5 mg	LORAZEPAM		Y
004846	003758	1 mg	LORAZEPAM		Y
004846	003759	2 mg	LORAZEPAM		Y
004846	016363	2 mg/mL	LORAZEPAM		Y
001616	003769	10 mg	OXAZEPAM		Y
001616	003770	15 mg	OXAZEPAM		Y
001616	003771	30 mg	OXAZEPAM		Y

Appendix 3. Error codes for denied claims

Error Code	Error Description
2017	RECIPIENT SERVICES COVERED BY HMO PLAN
4002	Non-Covered Drug
576	CLAIM HAS THIRD-PARTY PAYMENT
4999	THIS DRUG IS COVERED BY MEDICARE PART D
2002	RECIPIENT NOT ELIGIBLE FOR HEADER DATE OF SERVICE
513	RECIPIENT NAME AND NUMBER DISAGREE
3343	Questionable TPL amount
643	INVALID OTHER COVERAGE CODE
238	RECIPIENT NAME IS MISSING
2807	MATCH CODE INVALID
2809	DOB IS INVALID
4007	NON-COVERED NDC DUE TO CMS TERMINATION
1016	NON-PARTICIPATING MANUFACTURER
2017	RECIPIENT SERVICES COVERED BY HMO PLAN
221	DAYS SUPPLY MISSING
219	QUANTITY DISPENSED IS MISSING
268	BILLED AMOUNT MISSING
222	DAYS SUPPLY INVALID
2808	DOB IS MISSING

Appendix 4. Medication Codes and Categories

PDL Class	HSN	Subcategory	Generic
Antidepressants	001638	MAOI	ISOCARBOXAZID

Antidepressants	001639	MAOI	PHENELZINE SULFATE
Antidepressants	033510	MAOI	SELEGILINE
Antidepressants	001640	MAOI	TRANYLCYPROMINE SULFATE
Antidepressants	036156	Other	BUPROPION HBR
Antidepressants	001653	Other	BUPROPION HCL
Antidepressants	011505	Other	MIRTAZAPINE
Antidepressants	009612	Other	NEFAZODONE HCL
Antidepressants	001652	Other	TRAZODONE HCL
STC 07	001620	Other	BUSPIRONE HCL
Antidepressants	010321	SSRI/SNRI	CITALOPRAM HYDROBROMIDE
Antidepressants	040202	SSRI/SNRI	DESVENLAFAXINE
Antidepressants	040692	SSRI/SNRI	DESVENLAFAXINE FUMARATE
Antidepressants	035420	SSRI/SNRI	DESVENLAFAXINE SUCCINATE
Antidepressants	026521	SSRI/SNRI	DULOXETINE HCL
Antidepressants	024022	SSRI/SNRI	ESCITALOPRAM OXALATE
Antidepressants	001655	SSRI/SNRI	FLUOXETINE HCL
Antidepressants	006338	SSRI/SNRI	FLUVOXAMINE MALEATE
Antidepressants	040632	SSRI/SNRI	LEVOMILNACIPRAN HCL
Antidepressants	021229	SSRI/SNRI	MILNACIPRAN HCL
Antidepressants	007344	SSRI/SNRI	PAROXETINE HCL
Antidepressants	025796	SSRI/SNRI	PAROXETINE MESYLATE
Antidepressants	006324	SSRI/SNRI	SERTRALINE HCL
Antidepressants	008847	SSRI/SNRI	VENLAFAXINE HCL
Antidepressants	037597	SSRI/SNRI	VILAZODONE HCL
Antidepressants	040637	SSRI/SNRI	VORTIOXETINE HYDROBROMIDE
Antidepressants	001643	TCA	AMITRIPTYLINE HCL
Antidepressants	001648	TCA	AMOXAPINE
Antidepressants	004744	TCA	CLOMIPRAMINE HCL
Antidepressants	001645	TCA	DESIPRAMINE HCL
Antidepressants	001650	TCA	DOXEPIN HCL
Antidepressants	001641	TCA	IMIPRAMINE HCL
Antidepressants	001642	TCA	IMIPRAMINE PAMOATE
Antidepressants	001651	TCA	MAPROTILINE HCL
Antidepressants	001644	TCA	NORTRIPTYLINE HCL
Antidepressants	001646	TCA	PROTRIPTYLINE HCL
Antidepressants	001649	TCA	TRIMIPRAMINE MALEATE
Antipsychotics, 1st Gen			CHLORPROMAZINE HCL
Antipsychotics, 1st Gen			FLUPHENAZINE HCL
Antipsychotics, 1st Gen			HALOPERIDOL
Antipsychotics, 1st Gen			HALOPERIDOL LACTATE

Antipsychotics, 1st Gen		LOXAPINE SUCCINATE
Antipsychotics, 1st Gen		PERPHENAZINE
Antipsychotics, 1st Gen		PIMOZIDE
Antipsychotics, 1st Gen		THIORIDAZINE HCL
Antipsychotics, 1st Gen		THIOTHIXENE
Antipsychotics, 1st Gen		THIOTHIXENE HCL
Antipsychotics, 1st Gen		TRIFLUOPERAZINE HCL
Antipsychotics, 2nd Gen		ARIPIPRAZOLE
Antipsychotics, 2nd Gen		ASENAPINE MALEATE
Antipsychotics, 2nd Gen		BREXPIPRAZOLE
Antipsychotics, 2nd Gen		CARIPRAZINE HCL
Antipsychotics, 2nd Gen		CLOZAPINE
Antipsychotics, 2nd Gen		LURASIDONE HCL
Antipsychotics, 2nd Gen		OLANZAPINE
Antipsychotics, 2nd Gen		PALIPERIDONE
Antipsychotics, 2nd Gen		PIMAVANSERIN TARTRATE
Antipsychotics, 2nd Gen		QUETIAPINE FUMARATE
Antipsychotics, 2nd Gen		RISPERIDONE
Antipsychotics, 2nd Gen		ZIPRASIDONE HCL
Antipsychotics, Parenteral	024551	ARIPIPRAZOLE
Antipsychotics, Parenteral	042595	ARIPIPRAZOLE LAUROXIL
Antipsychotics, Parenteral	001621	CHLORPROMAZINE HCL
Antipsychotics, Parenteral	001624	FLUPHENAZINE DECANOATE
Antipsychotics, Parenteral	001626	FLUPHENAZINE HCL
Antipsychotics, Parenteral	001660	HALOPERIDOL DECANOATE
Antipsychotics, Parenteral	001661	HALOPERIDOL LACTATE
Antipsychotics, Parenteral	011814	OLANZAPINE
Antipsychotics, Parenteral	036716	OLANZAPINE PAMOATE
Antipsychotics, Parenteral	036479	PALIPERIDONE PALMITATE
Antipsychotics, Parenteral	025509	RISPERIDONE MICROSPHERES
Antipsychotics, Parenteral	001630	TRIFLUOPERAZINE HCL
Antipsychotics, Parenteral	023379	ZIPRASIDONE MESYLATE
Muscle Relaxants, Oral		BACLOFEN
Muscle Relaxants, Oral		CARISOPRODOL
Muscle Relaxants, Oral		CARISOPRODOL/ASPIRIN
Muscle Relaxants, Oral		CARISOPRODOL/ASPIRIN/CODEINE
Muscle Relaxants, Oral		CHLORZOXAZONE
Muscle Relaxants, Oral		CYCLOBENZAPRINE HCL
Muscle Relaxants, Oral		DANTROLENE SODIUM
Muscle Relaxants, Oral		METAXALONE

Muscle Relaxants, Oral	METHOCARBAMOL
Muscle Relaxants, Oral	METHOCARBAMOL/ASPIRIN
Muscle Relaxants, Oral	ORPHENADRINE CITRATE
Muscle Relaxants, Oral	ORPHENADRINE/ASPIRIN/CAFFEINE
Muscle Relaxants, Oral	TIZANIDINE HCL
Opioids, Long-Acting	BUPRENORPHINE
Opioids, Long-Acting	BUPRENORPHINE HCL
Opioids, Long-Acting	FENTANYL
Opioids, Long-Acting	HYDROCODONE BITARTRATE
Opioids, Long-Acting	HYDROMORPHONE HCL
Opioids, Long-Acting	LEVORPHANOL TARTRATE
Opioids, Long-Acting	METHADONE HCL
Opioids, Long-Acting	MORPHINE SULFATE
Opioids, Long-Acting	MORPHINE SULFATE/NALTREXONE
Opioids, Long-Acting	OXYCODONE HCL
Opioids, Long-Acting	OXYCODONE MYRISTATE
Opioids, Long-Acting	OXYMORPHONE HCL
Opioids, Long-Acting	TAPENTADOL HCL
Opioids, Long-Acting	TRAMADOL HCL
Opioids, Short-Acting	ACETAMINOPHEN WITH CODEINE
Opioids, Short-Acting	ACETAMINOPHEN/CAFF/DIHYDROCOD
Opioids, Short-Acting	ASPIRIN/CAFFEIN/DIHYDROCODEINE
Opioids, Short-Acting	ASPIRIN/CAFFEINE/DIHYDROCODEIN
Opioids, Short-Acting	ASPIRIN/CODEINE PHOSPHATE
Opioids, Short-Acting	BUTALBIT/ACETAMIN/CAFF/CODEINE
Opioids, Short-Acting	BUTORPHANOL TARTRATE
Opioids, Short-Acting	COD/ASA/SALICYLMD/ACETAMIN/CAF
Opioids, Short-Acting	CODEINE SULFATE
Opioids, Short-Acting	CODEINE/BUTALBITAL/ASA/CAFFEIN
Opioids, Short-Acting	FENTANYL
Opioids, Short-Acting	FENTANYL CITRATE
Opioids, Short-Acting	HYDROCODONE BITARTRATE/ASPIRIN
Opioids, Short-Acting	HYDROCODONE/ACETAMINOPHEN
Opioids, Short-Acting	HYDROCODONE/IBUPROFEN
Opioids, Short-Acting	HYDROMORPHONE HCL
Opioids, Short-Acting	IBUPROFEN/OXYCODONE HCL
Opioids, Short-Acting	MEPERIDINE HCL
Opioids, Short-Acting	MEPERIDINE HCL/PROMETH HCL
Opioids, Short-Acting	MORPHINE SULFATE
Opioids, Short-Acting	OPIUM/BELLADONNA ALKALOIDS

Opioids, Short-Acting	OXYCODONE HCL
Opioids, Short-Acting	OXYCODONE HCL/ACETAMINOPHEN
Opioids, Short-Acting	OXYCODONE HCL/ASPIRIN
Opioids, Short-Acting	OXYMORPHONE HCL
Opioids, Short-Acting	PENTAZOCINE HCL/NALOXONE HCL
Opioids, Short-Acting	PROPOXYPHENE HCL
Opioids, Short-Acting	PROPOXYPHENE HCL/ACETAMINOPHEN
Opioids, Short-Acting	PROPOXYPHENE NAP/ACETAMINOPHEN
Opioids, Short-Acting	PROPOXYPHENE/ASPIRIN/CAFFEINE
Opioids, Short-Acting	TAPENTADOL HCL
Opioids, Short-Acting	TRAMADOL HCL
Opioids, Short-Acting	TRAMADOL HCL/ACETAMINOPHEN
Sedatives	CHLORAL HYDRATE
Sedatives	DIPHENHYDRAMINE HCL
Sedatives	DOXEPIN HCL
Sedatives	DOXYLAMINE SUCCINATE
Sedatives	ESTAZOLAM
Sedatives	ESZOPICLONE
Sedatives	FLURAZEPAM HCL
Sedatives	MIDAZOLAM HCL
Sedatives	QUAZEPAM
Sedatives	RAMELTEON
Sedatives	SUVOREXANT
Sedatives	TASIMELTEON
Sedatives	TEMAZEPAM
Sedatives	TRIAZOLAM
Sedatives	ZALEPLON
Sedatives	ZOLPIDEM TARTRATE

Appendix 5. ICD-10 Diagnosis codes

Funded Category	ICD-10
Epilepsy	G40.001-G40.919
Epilepsy	R56.00-R56.9
Epilepsy	G93.81
Epilepsy	G83.8
Epilepsy	P90
Malignant Neoplasm or other end of life diagnosis	C00.0-C96.9
Malignant Neoplasm or other end of life diagnosis	Z51.5
Anxiety disorders	F40.10-F40.11
Anxiety disorders	F40.210-F40.9

Anxiety disorders	F41.1-F41.9
Panic disorder	F40.00-F40.02
Panic disorder	F41.0
Schizophrenic disorders	F20.0-F20.5
Schizophrenic disorders	F20.81-F20.9
Schizophrenic disorders	F25.0-F25.9
Schizophrenic disorders	F21
Depression or other mood disorder	F32.0-F33.9
Depression or other mood disorder	F34.0
Depression or other mood disorder	F34.1
Depression or other mood disorder	F34.81-F34.89
Depression or other mood disorder	F39
Depression or other mood disorder	N94.3
PTSD or acute stress disorder	F43.0-F43.12
PTSD or acute stress disorder	R45.7
Bipolar disorder	F31.0-F31.9
Bipolar disorder	F30.10-F30.9
Substance Abuse	F10.10-F10.11
Substance Abuse	F10.20-F10.21
Substance Abuse	F11.10-F11.11
Substance Abuse	F11.20-F11.21
Substance Abuse	F12.10-F12.11
Substance Abuse	F12.20-F12.21
Substance Abuse	F13.10-F13.11
Substance Abuse	F13.20-F13.21
Substance Abuse	F14.10-F14.11
Substance Abuse	F14.20-F14.21
Substance Abuse	F15.10-F15.11
Substance Abuse	F15.20-F15.21
Substance Abuse	F16.10-F16.11
Substance Abuse	F16.20-F16.21
Substance Abuse	F18.10-F18.11
Substance Abuse	F18.20-F18.21
Substance Abuse	F19.10-F19.11
Substance Abuse	F19.20-F19.21
Substance Abuse	Z71.51
<u>Unfunded Diagnoses by Category</u>	
Insomnia	F10.182
Insomnia	F10.282
Insomnia	F10.982

Insomnia	F11.182
Insomnia	F11.282
Insomnia	F11.982
Insomnia	F13.182
Insomnia	F13.282
Insomnia	F13.982
Insomnia	F14.182
Insomnia	F14.282
Insomnia	F14.982
Insomnia	F15.182
Insomnia	F15.282
Insomnia	F15.982
Insomnia	F19.182
Insomnia	F19.282
Insomnia	F19.982
Insomnia	F51.01-F51.9
Insomnia	G25.70-G25.81
Insomnia	G25.89
Insomnia	G26
Insomnia	G47.00-G47.29
Insomnia	G47.32
Insomnia	G47.50-G47.51
Insomnia	G47.53-G47.9
Fibromyalgia and chronic pain	M79.7
Fibromyalgia and chronic pain	G89.21
Fibromyalgia and chronic pain	G89.28-G89.29
Back and spine conditions	F45.42
Back and spine conditions	G83.4
Back and spine conditions	G95.0
Back and spine conditions	M24.08
Back and spine conditions	M25.78
Back and spine conditions	M40.00-M40.15
Back and spine conditions	M40.202-M40.57
Back and spine conditions	M42.00-M42.09
Back and spine conditions	M42.11-M42.9
Back and spine conditions	M43.00-M43.4
Back and spine conditions	M43.5X2-M43.5X9
Back and spine conditions	M43.8X1-M43.9
Back and spine conditions	M45.0-M45.9
Back and spine conditions	M46.1

Back and spine conditions	M46.40-M46.99
Back and spine conditions	M47.011-M47.9
Back and spine conditions	M48.00-M48.05
Back and spine conditions	M48.061-M48.38
Back and spine conditions	M48.8X1-M48.9
Back and spine conditions	M49.80-M49.89
Back and spine conditions	M50.00-M50.01
Back and spine conditions	M50.020-M50.93
Back and spine conditions	M51.04-M51.9
Back and spine conditions	M53.2X1-M53.9
Back and spine conditions	M54.00-M54.9
Back and spine conditions	M62.830
Back and spine conditions	M96.1-M96.4
Back and spine conditions	M99.00-M99.09
Back and spine conditions	M99.20-M99.79
Back and spine conditions	M99.81-M99.84
Back and spine conditions	Q06.0-Q06.3
Back and spine conditions	Q06.8-Q06.9
Back and spine conditions	Q68.0
Back and spine conditions	Q76.0-Q76.2
Back and spine conditions	Q76.411-Q76.49
Back and spine conditions	S13.0XXA-S13.0XXD
Back and spine conditions	S13.4XXA-S13.4XXD
Back and spine conditions	S13.8XXA-S13.8XXD
Back and spine conditions	S13.9XXA-S13.9XXD
Back and spine conditions	S16.1XXA-S16.1XXD
Back and spine conditions	S23.0XXA-S23.0XXD
Back and spine conditions	S23.100A-S23.100D
Back and spine conditions	S23.101A-S23.101D
Back and spine conditions	S23.110A-S23.110D
Back and spine conditions	S23.111A-S23.111D
Back and spine conditions	S23.120A-S23.120D
Back and spine conditions	S23.121A-S23.121D
Back and spine conditions	S23.122A-S23.122D
Back and spine conditions	S23.123A-S23.123D
Back and spine conditions	S23.130A-S23.130D
Back and spine conditions	S23.131A-S23.131D
Back and spine conditions	S23.132A-S23.132D
Back and spine conditions	S23.133A-S23.133D
Back and spine conditions	S23.140A-S23.140D

Back and spine conditions	S23.141A-S23.141D
Back and spine conditions	S23.142A-S23.142D
Back and spine conditions	S23.143A-S23.143D
Back and spine conditions	S23.150A-S23.150D
Back and spine conditions	S23.151A-S23.151D
Back and spine conditions	S23.152A-S23.152D
Back and spine conditions	S23.153A-S23.153D
Back and spine conditions	S23.160A-S23.160D
Back and spine conditions	S23.161A-S23.161D
Back and spine conditions	S23.162A-S23.162D
Back and spine conditions	S23.163A-S23.163D
Back and spine conditions	S23.170A-S23.170D
Back and spine conditions	S23.171A-S23.171D
Back and spine conditions	S23.3XXA-S23.3XXD
Back and spine conditions	S23.8XXA-S23.8XXD
Back and spine conditions	S23.9XXA-S23.9XXD
Back and spine conditions	S33.0XXA-S33.0XXD
Back and spine conditions	S33.100A-S33.100D
Back and spine conditions	S33.101A-S33.101D
Back and spine conditions	S33.110A-S33.110D
Back and spine conditions	S33.111A-S33.111D
Back and spine conditions	S33.120A-S33.120D
Back and spine conditions	S33.121A-S33.121D
Back and spine conditions	S33.130A-S33.130D
Back and spine conditions	S33.131A-S33.131D
Back and spine conditions	S33.140A-S33.140D
Back and spine conditions	S33.141A-S33.141D
Back and spine conditions	S33.5XXA-S33.5XXD
Back and spine conditions	S33.8XXA-S33.8XXD
Back and spine conditions	S33.9XXA-S33.9XXD
Back and spine conditions	S34.3XXA-S34.3XXD
Back and spine conditions	S39.092A-S39.092D
Back and spine conditions	S39.82XA-S39.82XD
Back and spine conditions	S39.92XA-S39.92XD
Benzodiazepine poisoning/adverse event	T424X1
Benzodiazepine poisoning/adverse event	T424X1A
Benzodiazepine poisoning/adverse event	T424X1D
Benzodiazepine poisoning/adverse event	T424X1S
Benzodiazepine poisoning/adverse event	T424X2
Benzodiazepine poisoning/adverse event	T424X2A

Benzodiazepine poisoning/adverse event	T424X2D
Benzodiazepine poisoning/adverse event	T424X2S
Benzodiazepine poisoning/adverse event	T424X4
Benzodiazepine poisoning/adverse event	T424X4A
Benzodiazepine poisoning/adverse event	T424X4D
Benzodiazepine poisoning/adverse event	T424X4S
Benzodiazepine poisoning/adverse event	T42.4X5
Benzodiazepine poisoning/adverse event	T42.4X5A
Benzodiazepine poisoning/adverse event	T42.4X5D
Benzodiazepine poisoning/adverse event	T42.4X5S
Benzodiazepine poisoning/adverse event	9694 (ICD-9)
Benzodiazepine poisoning/adverse event	E9394 (ICD-9)
Benzodiazepine poisoning/adverse event	E8532 (ICD-9)
Sedative poisoning, (unintentional, intentional, or undetermined; excludes assault, adverse effects, and underdosing)	T40.0xxx-T40.4xxx, T40.6xxx, T41.41xx-T41.44xx, T42.3xxx-T24.4xxx; T43.0xxx-T43.024x; T48.1xxx; T48.3xxx-T48.5xxx; T48.9xxx; T51.0xxx-T51.2xxx; T51.8xxx-T51.9xxx; T42.6xxx-T42.7xxx (excluding assault diagnoses Txx.xx3x, adverse events Txx.xx5x, and underdosing Txx.xx6x)
Sedative poisoning, accidental poisoning, undeterm pois, (benzodiazepine, barbiturates, other anesthetics, muscle relaxants, cold drugs, respir drugs NEC/NOS, alcohols, heroin, opioids, analgesics, psychotropic, sedatives)	9090, 9091, 9663, 9670, 9689, 9694, 9752, 9754, 9755, 9756, 9758, 9779, 9799, 9800, 9801, 9802, 9808, 9809, 96500, 96501, 96502, 96509, 980, E8501, E850, E8500, E8502, E8508, E8509, E851, E852, E8525, E8528, E8529, E853, E8530, E8531, E8532, E8538, E8539, E8551, E8558, E8559, E8586, E860, E8600, E8601, E8602, E8603, E8608, E8609, E9500, E9800, E9501, E9502, E9800, E9801, E9802, E9804, E9805, E9500, E9501, E9502, E9503, E9504, E9505 (ICD-9)

Appendix 6. Health Outcome Codes

ED Visits	Procedure Codes OR	99281-99285, 99288
	Revenue Center Codes	0450-0459 or 0981
Hospitalizations	Claim Type = I	Claim Type = I
Medical claims for naloxone administration	CPT Code	J2310

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
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OHSU Drug Effectiveness Review Project Summary Report – Benzodiazepines

Date of Review: September 2018 **Literature Search:** 9/1/2016-4/27/2018

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

Research Questions:
1. What are the comparative benefits and harms of benzodiazepines to treat mental illnesses compared with other treatments?
2. What are the benefits and harms of co-prescribing benzodiazepines and opioid narcotics in the outpatient setting?
3. What is the evidence for the tapering of benzodiazepines?
4. How do these outcomes vary by specific drug(s) used, patient characteristics (e.g., demographics, severity of illness), co-interventions, duration of treatment, etc.?

Conclusions:
- For treatment of panic disorder, there was low quality evidence that benzodiazepines had statistically improved response rates compared to tricyclic antidepressants (TCAs; relative risk [RR] 1.13; 95% confidence interval [CI] 1.01 to 1.27).[1,2] Response rates from individual studies included in the analysis ranged from 48 to 90% for benzodiazepines and from 20 to 86% for tricyclic antidepressants.[2] Evidence is limited as there was high heterogeneity between studies (I^2>95%), there was no difference in response rates between groups upon multiple sensitivity analyses, and studies failed to adequately define how treatment response was evaluated. There was insufficient evidence comparing benzodiazepines to first-line pharmacological treatments for panic disorder including selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs).[1]
- There was low quality evidence that fewer patients treated with benzodiazepines for general anxiety disorder discontinued treatment compared to TCAs (primarily imipramine and clomipramine; RR 0.40; 95% CI 0.29 to 0.57).[1] Treatment discontinuation due to adverse events and absolute difference in discontinuation rates were not reported though rates of discontinuation in individual trials ranged from 5-35% with benzodiazepines compared to 6-50% with TCAs.[2] A similar trend was observed in patients for treatment of depression (RR 0.84; mean difference [MD] -0.04 [95% CI -0.07 to 0.00]; number needed to harm [NNH] 25 [95% CI 14 to 100], I^2 = 35%).[1,3] However, most trials examined comparisons to older antidepressants and did not include comparisons to SSRIs or SNRIs.
- For treatment of general anxiety disorder, there was low quality evidence of no difference in treatment response between antidepressants (SSRIs, SNRIs, or TCAs) and benzodiazepines over 4 to 8 weeks.[1] Evidence was limited by conflicting evidence and lack of reported data. Similarly, there was insufficient evidence for other anxiety disorders including mixed anxiety disorders and social phobias.
- For treatment of depression, evidence was limited to comparisons of alprazolam to TCAs. No difference was observed in average symptom severity score, but fewer patients treated with alprazolam achieved a 50% reduction in score compared to TCAs (MD -0.11, 95% CI -0.24 to 0.01; I^2 = 58%; number needed to treat [NNT] 9, 95% CI 4 to 100; low quality evidence).[1,3]

- There is insufficient evidence to assess efficacy of benzodiazepines for treatment of post-traumatic stress disorder (PTSD). Guidelines from the Veterans Administration and Department of Defense recommend against use of benzodiazepines in this population due to the limited evidence regarding efficacy and risks associated with therapy.[4]
- Evidence for treatment of schizophrenia only included comparison of benzodiazepines to older antipsychotics (primarily haloperidol and chlorpromazine) and was limited by methodological flaws and risk of bias. Evidence was insufficient to determine differences in response rate or patient discontinuation due to adverse events within 0.5-12 hours or within 2-4 weeks of treatment.[1] Treatment with benzodiazepines or combination treatment with a benzodiazepine and antipsychotic did result in greater short-term sedation (at 20-40 minutes after administration) compared to use of an antipsychotic alone (RR 1.13 to 2.25).[1]
- Low quality evidence from observational studies indicates that concomitant use of benzodiazepines and opioid medications may be associated with increased risk of death.[1] Due to the retrospective nature of these data, the exact risk associated with concomitant benzodiazepine and opioid use is unclear.
- Evidence supporting tapering of benzodiazepines included 4 systematic reviews including more than 16,000 patients.[1,5,6] In general, patients who utilized tapering alone, tapering combined with psychological interventions, patient education or medical substitution had greater cessation rates (combined mean of 60%, range 25 to 85%) compared to usual care (range 9 to 21%).[1] The most common tapering methods used were a 25% reduction in dose every 1-2 weeks.[1]
- Overall, there was insufficient evidence to assess long-term efficacy or safety of benzodiazepines for mental health conditions and insufficient evidence to assess safety or efficacy in specific patient populations.

Recommendations:

- Current evidence for these agents does not support specific changes to the current Preferred Drug List (PDL). Update prior authorization criteria to limit use for treatment of PTSD, allow patients receiving long-term therapy time to taper the dose when appropriate, and require prescribers to provide supporting medical literature and/or appropriate rationale for long-term benzodiazepine use (**Appendix 3**).

Summary of Prior Reviews and Current Policy:

Despite lack of evidence supporting long-term benzodiazepine use and guidelines recommending only short-term use, benzodiazepines are often utilized for long-term treatment. In a previous analysis of the OHP population, approximately 37% of patients were prescribed benzodiazepines longer than 90 days (mean length of long-term use was 8.5 months).[7] Current utilization is presented in the accompanying policy evaluation. Benzodiazepines are FDA indicated for treatment of alcohol withdrawal, epilepsy, anxiety and panic disorder, and are often used off-label for other mental health conditions including bipolar disorder and schizophrenia. In an effort to prevent inappropriate long-term benzodiazepine use, a policy was implemented in July 2016 to require prior approval for benzodiazepine durations exceeding 4 weeks. The policy was intended to apply only to patients newly started on a benzodiazepine (no history within the last 120 days), and all patients with a history of benzodiazepine use prior to policy implementation were grandfathered at their current dose. Approval would be granted for new starts in any of the three situations for patients newly prescribed benzodiazepines:

1. Diagnosis of malignant neoplasm or other end of life diagnosis
2. Diagnosis of epilepsy
3. OHP-funded indication and all of the following
    a. Clinical rationale to support long-term benzodiazepine use for the supplied indication(s)
    b. No history of substance abuse and no concurrent sedative/hypnotic or opioid use

Methods:
The February 2017 drug class report on benzodiazepines by the Drug Effectiveness Review Project (DERP) at the Pacific Northwest Evidence-based Practice Center at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class. The DERP is part of the Pacific Northwest Evidence-based Practice Center at Oregon Health & Science University. The purpose of the DERP reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. DERP reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. OHSU does not recommend or endorse any guideline or recommendation developed by users of these reports. The original DERP report is available to Oregon Pharmacy and Therapeutics Committee members upon request. An executive summary report is publically available in the agenda packet and on the DURM website.

In addition, new systematic reviews and randomized controlled trials (RCTs) published since completion of the DERP report were identified. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. 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. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence in this document 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.

DERP Summary Findings:
<u>Efficacy and safety of benzodiazepines for mental illness</u>

- Anxiety and panic disorder
    - Evidence for the use of benzodiazepines for anxiety disorders included 3 systematic reviews (2871 patients) which examined efficacy of a benzodiazepine to another active medication. Comparators included TCAs (18 RCTs), SSRIs (2 RCTs), venlafaxine (2 RCTs), buspirone (3 RCTs), and pregabalin (2 RCTs).[1] On average, trials included in these reviews were 4 to 8 weeks in duration.[1] Outcomes evaluated in these trials included 50% improvement in the Hamilton Anxiety scale (HAM-A), general improvement in symptoms, remission, adverse events, and tolerability.[1] The HAM-A scale evaluates symptom severity on a scale of 0 to 55 points with larger values indicating more severe symptoms.[1]
    - Compared to TCAs, benzodiazepines had no clear differences in efficacy or safety in patients with general anxiety disorder. Change in overall symptoms was not reported, and evidence regarding specific symptoms was mixed. Differences in somatic symptoms were improved with alprazolam compared to imipramine, but imipramine reduced anxiety symptoms more than diazepam. Similar rates of adverse events were reported between groups. In patients with panic disorder, benzodiazepines had statistically improved response rates compared to TCAs (RR 1.13; 95% CI 1.01 to 1.27).[1] Evidence is limited as studies failed to report the absolute difference between groups or adequately define how response was evaluated.[1,2] Response rates from individual studies included in the analysis ranged from 48 to 90% for benzodiazepines and from 20 to 86% for antidepressants.[2] The proportion of patients who dropped out of the study (RR 0.40; 95% CI 0.29 to 0.57) and the proportion of patients with any adverse event (odds ratio [OR] 0.41; 95% CI 0.34 to 0.50) was also lower with benzodiazepines compared to TCAs.[1] The absolute difference in safety endpoints was not reported though the proportion of patients who discontinued the study ranged from 5-35% with benzodiazepines compared to 6-50% with

antidepressants upon analysis of individual studies.[2] Similar results were reported for the proportion of patients with any adverse event rates with 2-15% of patients treated with a benzodiazepine reporting adverse events compared to 6-40% of patients treated with TCAs.[2] All analyses were limited by high heterogeneity (I^2 >95%) between trials, and there was no difference in response rates between groups upon multiple sensitivity analyses.[1]
    - Upon direct comparison of buspirone with benzodiazepines, there was no clinically meaningful difference in the HAM-A scale between groups; the mean difference (MD) in HAM-A score compared to buspirone was 1.1 points with lorazepam (p=0.008), 1.1 points with alprazolam (p=0.009), and -0.2 points with diazepam (p=0.98).[1]
    - Evidence for other anxiety disorders including mixed anxiety disorders and social phobias was conflicting and based on a limited population of patients. No conclusive differences between benzodiazepines and other treatments could be determined.
    - Compared to placebo in 2 RCTs, patients treated with lorazepam had greater response rates at 4 to 8 weeks (OR 0.40; 95% CI 0.24 to 0.66).[1] Response was defined as more than 50% improvement in the HAM-A scale from baseline, and the average change in score was not reported.
- Depression
    - Evidence for alprazolam was evaluated in a high-quality systematic review which included direct comparisons to TCAs in 20 RCTs (n=1765) and comparison to placebo in 7 RCTs (n=770).[1] The majority of trials were 4-6 weeks in duration with an average dose of 2.9 mg alprazolam (range 1.5 to 8 mg) and TCAs within the therapeutic range.[1] The primary outcome examined improvement in the Hamilton depression scale.[1] Compared to TCAs, alprazolam had no difference in average symptom severity (MD 0.25 points; 95% CI -0.93 to 1.43, I^2=55%) though response rate (defined as the proportion of patients with a 50% relative improvement in score) was slightly lower with alprazolam compared to TCAs (MD -0.11, 95% CI -0.24 to 0.01; I2 = 58%; NNT 9, 95% CI 4 to 100).[1,3]
    - Compared to TCAs, there was a trend of fewer overall treatment discontinuations with alprazolam (RR 0.84; MD -0.04 [95% CI -0.07 to 0.00]; NNH 25 [95% CI 14 to 100], I^2 = 35%), and fewer patients treated with alprazolam discontinued treatment due to adverse events (RR 0.62; MD -0.04 [95% CI -0.08 to 0.01]; I2 =60%; NNH 25 [95% CI 11 to 100]).[1,3]
    - Compared to placebo, symptoms improvement evaluated with the Hamilton depression scale (MD -5.34; 95% CI -7.48 to 3.2; I^2 = 68%) and response rate defined as 50% reduction in Hamilton depression score (MD 0.32; 95% CI 0.22 to 0.42, I^2 = 0%; NNT 3) were improved with alprazolam.[1,3] There was no difference in withdrawal due to adverse events.
- Post-Traumatic Stress Disorder (PTSD)
    - Evidence for benzodiazepine use in patients with PTSD was limited to a Cochrane review which included a single, small RCT of temazepam 30 mg versus placebo (n=22) over 1 week.[1] Patients were on average 36 years of age and initiated treatment within 2 weeks after a traumatic event.[1] The proportion of patients who met diagnostic criteria for PTSD at 6 weeks was actually higher in those treated with temazepam (55%) compared to placebo (27%), though results failed to achieve statistical significance (p=0.387).[1] No difference was reported in symptom severity or adverse events.[1]
- Schizophrenia
    - Evidence for benzodiazepine use in schizophrenia included a single systematic review of 34 RCTs (n=2657 patients).[1] Thirteen RCTs examined benzodiazepines (most commonly diazepam, clonazepam, lorazepam and chlordiazepoxide) compared to an antipsychotic drug (most commonly haloperidol and chlorpromazine), 20 RCTs assessed benzodiazepines in combination with antipsychotics, and 7 RCTs compared benzodiazepines to placebo.[1] Overall trials were limited by small populations (12-301 patients), short duration (1-10 weeks), and important outcome reporting flaws.[1]
    - Compared to antipsychotics, there was no difference in response rate or patient discontinuation due to adverse events within 0.5-12 hours or within 2-4 weeks of treatment.[1] Similarly, when used in combination with antipsychotics, benzodiazepines were not significantly different than antipsychotics alone upon follow-up of 1 to 10 weeks.[1] The only difference observed with benzodiazepines was increased short-term sedation with

benzodiazepines (RR 1.32 at 20 minutes and RR 1.13 at 40 minutes) or combination benzodiazepine and antipsychotic (RR 2.25 at 30 minutes and RR 1.39 at 60 minutes) compared with antipsychotics alone.[1]

- Compared with placebo (6 RCTs, n=382 patients), there was no difference in clinically important response rate, rate of relapse, or study discontinuation with short-term treatment.[1] Patients treated with benzodiazepines more commonly reported adverse events including loss of energy and ataxia compared to placebo (ARR 21%; RR 1.44 [95% CI 1.02 to 2.04]; NNH 5 [95% CI 3 to 50]).[1,8]

Co-prescribing of benzodiazepines and opioids

Evidence assessing the benefits and harms of co-prescribing benzodiazepines and opioids included one high-quality systematic review and 2 clinical guidelines with recommendations regarding concomitant use of these medications (Centers for Disease Control and American Society of Interventional Pain Physicians).[1] The review included evidence from 71 studies related to unintended methadone overdose though only 1 systematic review, 2 retrospective cohort studies (n=5540), and 5 case series (n=1127) specifically addressed safety of concomitant benzodiazepines and methadone.[1] Co-prescribing of these medications was associated with increased risk of drug-related deaths in 2 retrospective cohort studies (adjusted hazard ratio [HR] 1.4; 95% CI 1.2 to 1.7 and HR 4.35; 95% CI 1.32 to 14.30).[1] Similarly, in 5 case series examining methadone overdose deaths, blood toxicology was positive for both benzodiazepines and methadone in 36 to 67% of deaths.[1] Due to the retrospective nature of these data, the exact risk associated with concomitant benzodiazepine and opioid is unclear.

Guidelines from the Centers for Disease Control recommend avoidance of concurrent opioids and benzodiazepines whenever possible, a recommendation based on one prospective cohort study and 1 retrospective study.[1] Guidelines from the American Society of Interventional Pain Physicians recommend evaluation of the contraindications to opioid use in chronic non-cancer pain including concomitant use of benzodiazepines based on fair to limited quality evidence.[1] Limited-evidence is described as evidence which is insufficient to assess effects on health outcomes, and fair evidence is described as evidence which is sufficient to determine effects on outcomes but strength is limited by size, number, or quality of trials, consistency of results, generalizability to practice, or use of surrogate outcomes.[1] Quality of these guidelines was assessed using the University of Pennsylvania's Center for Evidence-Based Practice Trustworthy Guideline criteria. Guidelines from the CDC met all quality metrics, but guidelines from the American Society of Interventional Pain Physicians were downgraded because they published in 2012, do not report conflicts of interest, and are only partially based on a systematic review of evidence.[1]

Methods of tapering benzodiazepines

Two systematic reviews of fair to good quality (evaluating a total of 60 studies of various types) were included in the review.[1] Trials were only included if they evaluated benzodiazepine use for greater than 3 months.[1] Mean age of participants ranged from 38 to 77 years and 45-81% of participants were female.[1] Interventions included various tapering regimens, informational or educational interventions, psychological interventions such as cognitive behavioral therapy, or medical substitution compared to normal or routine care. The primary outcome was complete discontinuation of benzodiazepines. In one systematic review, patients who utilized tapering alone, tapering combined with psychological interventions, or tapering plus medical substitution had greater cessation rates (combined mean of 60%, range 25 to 85%) compared to usual care (range 9 to 21%).[1] Stratification by dose (less than or greater than 10 mg/day diazepam equivalents) or duration of use (less than or greater than 7 years) demonstrated no differences in treatment success with cessation rates of 48-61%.[1] In the second review, addition of psychological treatment improved cessation rates compared to tapering alone (OR 1.82; 95% CI 1.25 to 2.67), but substitutive pharmacology failed to demonstrate a significant difference in rates.[1] In addition, tapering plus abrupt substitutive pharmacotherapy was less effective than tapering alone (OR 0.30; 95% CI 0.14 to 0.64).[1] Regarding adverse effects, withdrawal symptoms were frequently reported in both reviews for more than 30% of patients, though no symptoms severe enough to require medical attention were recorded.[1] The most common tapering methods used were a 25% reduction in dose every 1-2 weeks.[1]

Other Systematic Reviews

A series of Cochrane reviews was published which included evidence regarding safety and effectiveness of benzodiazepines for mental health conditions. The first examined evidence for psychological interventions compared to pharmacologic interventions (including antidepressants and benzodiazepines) for treatment of panic disorder in adults.[9] Four trials were included which examined psychological therapies compared to either diazepam or alprazolam.[9] Data was significantly limited by lack of reported methods for these trials with unclear randomization methods, unblinded groups, selective reporting, and conflicts of interest. Psychological interventions included cognitive behavioral therapy, psychodynamic therapies (focus on revealing and resolving intrapsychic or unconscious conflicts), psychoeducation, and behavior therapy.[9] Overall, there was no difference in short-term response, short-term remission, short-term improvement within 6 months of treatment initiation, or treatment discontinuation for any reason.[9] Similar results were observed upon comparison of psychological therapies compared to antidepressants alone or combination treatment with antidepressants and benzodiazepines.[9]

The second Cochrane review compared evidence regarding efficacy and safety of pharmacologic treatments for panic disorder in adults (including benzodiazepines, TCAs, SSRIs, and SNRIs).[10] For all outcomes, evidence was of low to insufficient quality. Primary outcomes included the proportions of patients that did not respond to treatment and the proportion who discontinued treatment.[10] Secondary outcomes included failure to remit, improvement in panic symptoms, anxiety or depression, frequency of panic attacks, and social functioning. Outcomes were reported on average at 12 weeks (study durations ranged from 2 to 6 months).[10] There was low quality evidence from 8 RCTs (n=2055), of no difference in the proportion of patients who responded to treatment between benzodiazepines and antidepressants.[10] Similar results were reported upon comparison of TCAs and SSRIs to benzodiazepines.[10] Evidence was limited by unclear risk of bias in included trials, though results were consistent between studies. A statistically greater proportion of participants treated with an antidepressant discontinued treatment compared to benzodiazepines (30% vs. 21%; RR 1.64; 95% CI 1.03 to 2.63).[10] However, due to wide confidence intervals, significant heterogeneity (I^2=75%), and unclear or high risk of bias, there was insufficient evidence to determine clinical differences in tolerability between groups. Similar results were observed for secondary outcomes with no difference between benzodiazepines and antidepressants, TCAs, or SSRIs.[10] There was also no difference upon direct comparison of diazepam to alprazolam and alprazolam to clonazepam in 2 RCTs (n=310).[10]

The third Cochrane report evaluated pharmacotherapy for social anxiety disorder.[11] Overall, there was insufficient direct evidence comparing benzodiazepines to other treatments, and placebo-controlled evidence was of low to insufficient quality for outcomes of interest.[11] Two RCTs provided low quality evidence that treatment response was improved with benzodiazepines compared to placebo (81% vs. 20%; RR 4.03; 95% CI 2.45 to 6.65, n=132) with no difference in treatment relapse or dropout rate.[11] Response rate was defined as a score of either 1 or 2 (much or very much improved) on the Clinical Global Impressions Improvement (CGI-I) scale (range 1-7).[11] Evidence for other secondary outcome measures including reduction in symptoms and associated disability was limited by high heterogeneity and/or small treatment effects.[11] Of note, only SSRIs demonstrated an improvement in preventing relapse compared to placebo (moderate quality evidence).[11] Authors recommend that potential benefits of benzodiazepines be considered within the context of potential for abuse and adverse effects.[11]

An AHRQ report examined evidence for treatment of anxiety in children.[12] Overall, there was insufficient direct comparative data of drug treatments for improvement in primary anxiety symptoms.[12] Compared to placebo, there was low quality evidence that benzodiazepines did not have any significant improvement in primary anxiety symptoms for children.[12] Evidence was based on a single small RCT with severe imprecision.[12]

A Cochrane review assessing pharmacological interventions to facilitate discontinuation in chronic benzodiazepine users found only insufficient to low quality of evidence that pharmacological substitution improves outcomes of benzodiazepine discontinuation, withdrawal symptoms, anxiety symptoms, or relapse to benzodiazepine use.[5] Medications assessed included valproate, pregabalin, tricyclic antidepressants, paroxetine, carbamazepine and flumazenil.[5] Data were

limited by high risk of bias, imprecision, small sample size, and variation between the types of interventions.[5] Similarly, there was insufficient evidence to assess harms associated with benzodiazepine discontinuation.[5] Authors concluded that it was not possible to draw firm conclusions regarding effectiveness or harms of pharmacological interventions for benzodiazepine discontinuation.[5]

A systematic review published in 2017 described methods used to discontinue benzodiazepines and other sedative hypnotics in patients older than 65 years of age.[6] Seven studies were included in the review and data were limited by small sample size and significant variation in studies.[6] Interventions typically included tapering in combination with provider outreach, pharmacological substitution, patient education, and/or psychological support.[6] Due to the wide variety of interventions and outcomes studied, results were described only descriptively. Pharmacologic substitution included use of trazodone, lometazepam (not available in the US), or melatonin.[6] When used with or without psychological support, rates of benzodiazepine discontinuation ranged from 40 to 80% compared to patients randomized to placebo.[6] Patient education was assessed in 2 studies and included a 1 hour lecture on safety of benzodiazepines including fall risk or a patient education booklet to facilitate discontinuation over 6 months. More patients discontinued treatment compared to usual care (treatment difference of 39% and 22% for each intervention).[6] One study described a discontinuation rate of 80% at 6 months with tapering and psychological support.[6] Overall, authors conclude that withdrawal of benzodiazepines and sedative medications is feasible with use of multiple interventions, but evidence on clinical outcomes was limited.[6]

Guidelines

Updated guidelines from the Veterans Administration and Department of Defense for the management of PTSD and acute stress disorder were published in 2017.[4] Recommended first-line pharmacotherapy for treatment of PTSD is sertraline, paroxetine, fluoxetine, or venlafaxine (strong recommendation).[4] Alternative options are nefazodone, imipramine, or phenelzine monotherapy if either the recommended first-line pharmacotherapy, trauma-focused psychotherapy or non-trauma-focused psychotherapy are ineffective, unavailable, or not tolerated (weak recommendation).[4] Guidelines recommend against the use of benzodiazepines (as monotherapy or combination therapy) for treatment of PTSD due to the lack of evidence supporting efficacy and known risks associated with treatment (strong recommendation).[4]

Guidelines from the European Sleep Research Society for the diagnosis and treatment of insomnia were published in 2017.[13] Cognitive behavioral therapy for insomnia (CBT-I) was recommended as the first-line treatment for chronic insomnia in adults (strong recommendation; high quality evidence).[13] Pharmacotherapy, including benzodiazepines and benzodiazepine receptor agonists are recommended only in the short-term (≤4 weeks) if CBT-I is ineffective or unavailable, and long-term treatment with pharmacotherapy should not be recommended due to lack of evidence and risk of adverse effects (strong recommendation; low quality evidence).[13] Relevant conflicts of interest were reported for nine members (35%) of the guideline committee. Industry-related payments for speaking engagements or advisory boards and consulting fees were disclosed for behavioral therapy companies (n=4) and pharmaceutical companies (n=5). One member held patents in a behavioral medicine company and one member had research funding from pharmaceutical companies.[13]

New Formulations or Indications:

None.

New FDA Safety Alerts:

Labeling for all benzodiazepines were updated in 2016 and 2017 to include a boxed warning for concomitant use of benzodiazepines and opioids.[14] Concomitant use may result in profound sedation, respiratory depression, coma and death.[14] Recommendations in package labeling include limitation to the minimum

necessary dose and duration, concomitant use only in patients for whom alternative treatment options have failed, and monitoring for respiratory depression and sedation.[14]

Randomized Controlled Trials:
A total of 113 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical).

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Appendix 1: Current Preferred Drug List

FormDesc	Brand	Generic	PDL	Carve-out
TABLET	CLONAZEPAM	CLONAZEPAM	Y	N
TABLET	KLONOPIN	CLONAZEPAM	Y	N
TAB RAPDIS	CLONAZEPAM	CLONAZEPAM	N	N
TABLET	ALPRAZOLAM	ALPRAZOLAM		Y
TAB ER 24H	ALPRAZOLAM ER	ALPRAZOLAM		Y
ORAL CONC	ALPRAZOLAM INTENSOL	ALPRAZOLAM		Y
TAB RAPDIS	ALPRAZOLAM ODT	ALPRAZOLAM		Y
TAB ER 24H	ALPRAZOLAM XR	ALPRAZOLAM		Y
TABLET	XANAX	ALPRAZOLAM		Y
TAB ER 24H	XANAX XR	ALPRAZOLAM		Y
TABLET	CHLORDIAZEPOXIDE-AMITRIPTYLINE	AMITRIPTYLINE/CHLORDIAZEPOXIDE		Y
CAPSULE	CHLORDIAZEPOXIDE HCL	CHLORDIAZEPOXIDE HCL		Y
CAPSULE	CHLORDIAZEPOXIDE-CLIDINIUM	CHLORDIAZEPOXIDE/CLIDINIUM BR		N
CAPSULE	LIBRAX	CHLORDIAZEPOXIDE/CLIDINIUM BR		N
TABLET	CLORAZEPATE DIPOTASSIUM	CLORAZEPATE DIPOTASSIUM		Y
TABLET	TRANXENE T-TAB	CLORAZEPATE DIPOTASSIUM		Y
ORAL CONC	DIAZEPAM	DIAZEPAM		Y
SOLUTION	DIAZEPAM	DIAZEPAM		Y
TABLET	DIAZEPAM	DIAZEPAM		Y
TABLET	VALIUM	DIAZEPAM		Y
TABLET	ATIVAN	LORAZEPAM		Y
ORAL CONC	LORAZEPAM	LORAZEPAM		Y
TABLET	LORAZEPAM	LORAZEPAM		Y
ORAL CONC	LORAZEPAM INTENSOL	LORAZEPAM		Y
CAPSULE	OXAZEPAM	OXAZEPAM		Y

Appendix 2: Literature Search

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to April 25 2018

1	exp Benzodiazepines/	64746
2	exp Mental Disorders/	1131000
3	exp Epilepsy/	150100
4	exp "Sleep Initiation and Maintenance Disorders"/	11278
5	2 or 3 or 4	1258866
6	1 and 5	20696
7	limit 6 to (english language and humans)	15095
8	limit 7 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv 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)	5321
9	limit 8 to yr="2016 -Current"	113

Benzodiazepines

Goal(s):

- Approve only for OHP-funded diagnoses.
- Prevent inappropriate long-term benzodiazepine use beyond 4 weeks for new starts (no history within the last 120 days).
- Approve long-term use only for indications supported by the medical literature.

Length of Authorization:

- 6 months to 12 months (criteria-specific)

Requires PA:

- All benzodiazepines used beyond 4 weeks. Short-term use does not require PA.

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have a malignant neoplasm or other end-of-life diagnosis (ICD10 C00.xx-D49.xx or Z51.5)?	**Yes:** Approve for 12 months	**No:** Go to #3
3. Is the diagnosis an OHP-funded diagnosis?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
~~3.~~4. Does the patient have a seizure disorder diagnosis? ~~(ICD10 G40.xx; F44.5; R56.9; G93.81; R56.1; R56.9; G93.81; G83.8; P90)?~~	**Yes:** Approve for 12 months	**No:** Go to #5

Approval Criteria		
~~Is the diagnosis an OHP-funded diagnosis?~~	~~**Yes:** Go to #5~~	~~**No:** Pass to RPh. Deny; not funded by the OHP.~~
5. Is the request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #6
6. Is the request for treatment of post-traumatic stress disorder (PTSD)? Note: Risks of benzodiazepine treatment outweigh benefits for patients with PTSD. Treatment with benzodiazepines is not recommended.	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #7
7. Is the request for treatment of anxiety or panic disorder?	**Yes:** Go to #8	**No:** Go to #9
~~4.~~8. Is the medication prescribed by or in consultation with a psychiatrist OR does the patient have a documented trial and failure, contraindication, intolerance, or inability to access recommended first-line treatment options including antidepressants AND psychotherapy (e.g. behavioral therapy, relaxation response training, mindfulness meditation training, eye movement desensitization and reprocessing)? Note: An adequate trial to determine efficacy of an SSRI or SNRI is 4-6 weeks.	**Yes:** Go to #11 Document trial, contraindication, or intolerance to treatment options.	**No:** Pass to RPh; Deny; medical appropriateness. Recommend adequate trial of first-line therapies. If provider requests short-term approval with a plan to start additional therapy, approval may be granted for up to 3 months. Subsequent requests must document experience with first-line treatment options.
9. Is the request for treatment of psychosis, schizophrenia or schizoaffective disorder?	**Yes:** Go to #10	**No:** Go to #11

Approval Criteria		
10. Is the medication prescribed by or in consultation with a psychiatrist OR does the patient have an adequate trial and failure, contraindication, intolerance, or inability to access recommended first-line treatment options including second-generation antipsychotics AND psychotherapy (e.g. counseling, cognitive behavioral therapy, social skills training, or psychoeducation)? Note: For continued symptoms, assess adherence and dose optimization. For patients on an adequate dose of antipsychotic, guidelines recommend trial of a second antipsychotic or augmentation with a mood stabilizer.	**Yes:** Go to #11 Document trial, contraindication, or intolerance to treatment options.	**No:** Pass to RPh; Deny; medical appropriateness. Recommend adequate trial of first-line therapies. If provider requests short-term approval with a plan to start additional therapy, approval may be granted for up to 3 months. Subsequent requests must document experience with first-line treatment options.
~~5.~~11. Is the patient on a concurrent sedative, hypnotic, muscle relaxant, or opioid?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #12
~~6.~~12. RPh only: Is there appropriate rationale to support long-term benzodiazepine use for this indication? For anxiety, panic disorder, or schizophrenia, provider rationale should include information from relevant chart notes. For other diagnoses, provider must document supporting medical literature.	**Yes:** Approve for up to 6 months.	**No:** Deny; medical appropriateness.

Renewal Criteria		
1. Is the request for a decrease in daily dose OR a change in drug with the intent to taper the dose?	**Yes:** Approve for up to 6 months or length of taper, whichever is less.	**No:** Go to #2
2. Is the request for an increase in dose?	**Yes:** Go to #3	**No:** Go to #4

Renewal Criteria		
3. Has the patient failed all clinically appropriate first-line adjunct treatment options OR, when applicable, is the patient adherent to recommended first-line treatment options for their condition?	**Yes:** Go to #4	**No:** Pass to RPh; Deny; medical appropriateness. Recommend trial of alternative therapies. If provider requests short-term approval with a plan to start additional therapy, approval may be granted for up to 3 months. Subsequent requests must document experience with first-line treatment options.
4. Is there documentation based on medical records that provider and patient have discussed whether benefits of long-term therapy (e.g. symptom improvement, social function, number of hospitalizations, etc) continue to outweigh risks of therapy (e.g. sedation, dependence, cognitive dysfunction and/or psychiatric instability)?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh; Deny; medical appropriateness. Recommend trial of gradual taper plan. Approval may be granted for up to 3 months to allow time to develop a taper plan. Subsequent requests must document progress toward taper.

P&T Review: *91/18(SS), 3/14*
Implementation: *TBD; 5/1/16*

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PA Update: Oral Cystic Fibrosis Modulators

Date of Review: September 2018

Conclusions:

- Lumacaftor/ivacaftor was recently approved for patients 2 to 5 years of age who are homozygous for the F508del mutation based on one 24-week, non-randomized, open-label safety and pharmacokinetic study.[1] There is insufficient evidence that lumacaftor/ivacaftor is effective in improving outcomes including lung function, quality of life, or pulmonary exacerbations in this patient population.
- Ivacaftor was FDA approved for children ages 12 to 24 months of age based one open-label, 24-week study demonstrating similar pharmacokinetic response and overall tolerability as seen in older children.[2,3] There is insufficient evidence that ivacaftor is effective in improving clinical outcomes including lung function, quality of life, or pulmonary exacerbations in this patient population. Although the approval includes any mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to ivacaftor, ivacaftor was only studied in 8 of the gating mutations.
- A significant safety concern for both lumacaftor/ivacaftor and ivacaftor in pediatric populations is elevated liver transaminases and the potential long-term impact of treatment on liver function. The incidence of increased liver transaminases in clinical trials in adults with ivacaftor was 6%, while this rate increased to 14.7% in patients ages 2 to 6 and 27.8% in those less than 24 months of age.[2] Treatment with lumacaftor/ivacaftor resulted in elevated liver transaminases in 19% of patients ages 2 to 5 years of age.[1]
- Tezacaftor/ivacaftor was FDA approved for patients who have at least one mutation in the CFTR gene that is responsive to therapy. This is based on one trial that included patients who were heterozygous for the F508del mutation with a second allele predicted to be responsive.[4] However, the FDA approval did not reflect this study population. The FDA division of drug information was not able to provide additional insight into the reasoning behind the specific FDA approval and language used in the drug label. The PA criteria has been updated to reflect the FDA approved indication.

Recommendations:

- Approve amended PA criteria to reflect updated FDA labeling based on approved indications.

New FDA Approved Indications:

1. In August 2018, lumacaftor/ivacaftor was FDA approved for patients 2 to 5 years of age who are homozygous for the F508del mutation. The previous FDA label was for patients 6 years of age and older.[1] There are approximately 1300 patients age 2 through 5 years of age homozygous for the F508del mutation in the United States. The approval was based on a 24-week, unpublished, phase 3, non-randomized, open-label trial in 60 patients aged 2 to 5 years with a mean baseline percent predicted forced expiratory volume at 1 second (ppFEV1) of 89.8%. The study was designed as a safety and pharmacokinetic study and was funded by Vertex Pharmaceuticals. Any clinically significant laboratory abnormality was an exclusion criterion of the study. Study results in their entirety are not available at this time on clinicaltrials.gov or in the FDA review documents. FDA approved the expanded

indication based on the study results that demonstrated treatment with the drug for 24 weeks was generally safe and well tolerated, with a safety profile similar to patients aged 6 years of age and older. The most common adverse event was cough (63%). Three patients discontinued treatment due to elevated liver enzymes. During the 24 weeks, the incidence of elevated liver transaminases greater than 8, greater than 5 and greater than 3 times the upper limit of normal (ULN) was 8.3% (5/60), 11.7% (7/60) and 15% (9/60).[1]

Additionally, there was a significant reduction in sweat chloride (-31.7 mmol/L; 95% CI -35.7 to -27.6). There was no correlation between decrease in sweat chloride and improvement in ppFEV1.

There is insufficient information available to fully assess this trial for quality or to assess the efficacy of lumacaftor/ivacaftor in this population on clinically important outcomes. Minimal study results are available from the package insert. Current prior authorization criteria requires medical director review for lumacaftor/ivacaftor if the patient is younger than 12 years of age based on an open-label study resulting in no difference in FEV1 in children ages 6 to 11 years and the safety concern of elevations in liver transaminases compared to what was seen in studies with adult patients (19.3% vs. 5%).

2. Also in August 2018, ivacaftor was FDA approved for children ages 12 to <24 months who have at least one mutation in the CFTR gene that is responsive to ivacaftor based on clinical and/or in in vitro assay data.[2] Approval is based on data from an ongoing phase 3 open-label safety and pharmacokinetic study (n=25) including children with one of 10 gating mutations (G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D or R117H).[3] Part A of the study assessed safety and pharmacokinetics after 4 days of treatment, while part B was a 24-week assessment of safety and exploratory efficacy outcomes. The study was funded by Vertex Pharmaceuticals, who had a role in study design, data collection, data analysis, data interpretation, and writing of the report. Seven children 12 to 24 months were enrolled in part A of the study. Six of these children had the G551D mutation on one allele. Only one of these children was eligible to continue to part B of the study. A total of 17 (94%) of children included in the 24-week assessment were younger than 24 months. A total of 18 (95%) of children experienced at least one treatment-emergent adverse event during the 24 weeks. The most common were cough, pyrexia, increased liver transaminases, otitis media and upper respiratory tract infection. Twenty eight percent (n=5) of children experienced increased concentrations of liver transaminases to more than three times the ULN. There were no discontinuations due to adverse events. The mean sweat chloride concentration decreased from baseline with a mean change of 73.5 mmol/l (95% CI -86 to -61). However, this outcome was only measured in ten subjects and study authors did not provide details on the remaining nine.

Oral Cystic Fibrosis Modulators

Goals:

- To ensure appropriate drug use and limit to patient populations in which they have demonstrated to be effective and safe.
- To monitor for clinical response for appropriate continuation of therapy.

Length of Authorization:

- 90 days to 6 months

Requires PA:

- Ivacaftor (Kalydeco®)
- Lumacaftor/Ivacaftor (Orkambi®)
- Tezacaftor/Ivacaftor (Symdeko®)

Preferred Alternatives:

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

Approval Criteria		
1. Is this a request for continuation of therapy previously approved by the FFS program (patient already on ivacaftor, lumacaftor/ivacaftor, or tezacaftor/ivacaftor)?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code. Go to #3	
3. Is the request from a practitioner at an accredited Cystic Fibrosis Center or a pulmonologist?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. How many exacerbations and/or hospitalizations in the past 12 months has the patient had?	Prescriber must provide documentation before approval. Document baseline value. Go to #5	
5. Is the request for ivacaftor?	**Yes:** Go to #6	**No:** Go to #10

Approval Criteria		
6. What is the patient's baseline sweat chloride level?	Prescriber must provide documentation before approval. Document baseline value. Go to #7	
7. Does the patient have a diagnosis of cystic fibrosis and is 12 months of age or older?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Does the patient have a documented mutation in the CFTR gene that ivacaftor is FDA approved for (see below)? FDA approved CFTR mutations include: E56K, G178R, S549R K1060T, G1244E, P67L, E193K, G551D, A1067T, S1251N R74W, L206W, G551S, G1069R, S1255P, D110E, R347H, D579G, R1070Q, D1270N, D110H, R352Q, S945L, R1070W G1349D, R117C, A455E, S977F, F1074L, R117H, S549N, F1052V, D1152H 3849 + 10kbC –T, 2789 +5G>A, 3272-26A-G, 711+3A-G, E831X	**Yes:** Go to #17	**No:** Go to #9 If unknown, there needs to be a CF mutation test to detect the presence of the CFTR mutation prior to use. CF due to other CFTR gene mutations are not approved indications (including the F508del mutation).
9. Does the patient have a documented R117H mutation in the CFTR gene detected by a CF mutation test?	**Yes:** Pass to RPh. Refer request to Medical Director for manual review and assessment of clinical severity of disease for approval.	**No:** Pass to RPh. Deny; medical appropriateness. If unknown, there needs to be a CF mutation test to detect the presence of the CFTR mutation prior to use. CF due to other CFTR gene mutations are not approved indications (including the F508del mutation).

Approval Criteria		
10. Is the request for lumacaftor/ivacaftor?	**Yes:** Go to #11	**No:** Go to #13
11. Does the patient have a diagnosis of cystic fibrosis and is 2 years of age or older?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness
12. Does the patient have a documented homozygous Phe508del mutation in the CFTR gene detected by an CF mutation test?	**Yes:** If the patient is younger than 12 years of age, refer case to OHP Medical Director; otherwise, Go to #17	**No:** Pass to RPh. Deny; medical appropriateness If unknown, there needs to be a CF mutation test to detect the presence of the CFTR mutation prior to use. CF due to other CFTR gene mutations are not approved indications (including those who are heterozygous for the F508del mutation)
13. Is the request for tezacaftor/ivacaftor?	**Yes:** Go to #14	**No:** Pass to RPh. Deny; medical appropriateness
14. Does the patient have a diagnosis of cystic fibrosis and is 12 years of age or older?	**Yes:** Go to #15	**No:** Pass to RPh. Deny; medical appropriateness
15. Does the patient have a documented homozygous Phe508del mutation in the CFTR gene detected by a CF mutation test?	**Yes:** Go to #17	**No:** Go to #16 If unknown, there needs to be a CF mutation test to detect the presence of the CFTR mutation prior to use.

Approval Criteria		
16. Does the patient have at least one mutation that is responsive to tezacaftor/ivacaftor based on in vitro data and FDA labeling? Note: A list of CFTR gene mutations that produce CFTR protein and are responsive to tezacaftor/ivacaftor include: A455E, A1067T, D110E, D110H, D579G, D1152H, D1270N, E56K, E193K, E831X, F1052V, F1074L, K1060T, L206W, P67L, R74W, R1070W, R117C, R347H, R352Q, S945L, S977F, 711+3A→G, 2789+5G→A, 3272-26A→G, 3849+10kbC→T	**Yes:** Go to #17	**No:** Pass to RPh. Deny; medical appropriateness. If unknown, there needs to be a CF mutation test to detect the presence of the CFTR mutation prior to use.
17. Is the patient on ALL the following drugs, or has had an adequate trial of each drug, unless contraindicated or not appropriate based on age <6 years and normal lung function: • Dornase alfa; AND • Hypertonic saline; AND • Inhaled or oral antibiotics (if appropriate)?	**Yes:** Go to #18	**No:** Pass to RPh. Deny; medical appropriateness
18. Is the patient on concomitant therapy with a strong CYP3A4 inducer (see Table 1)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #19
19. What are the baseline liver function (AST/ALT) and bilirubin levels (within previous 3 months)?	Document labs. Go to #20 If unknown, these labs need to be collected prior to approval.	

Approval Criteria		
20. Is medication dosed appropriately based on age, weight, and co-administered drugs (see dosing and administration below)?	**Yes:** Approve for 90 days. Note: Approve for 90 days to allow time for patient to have a sweat chloride test done after 30 days of treatment if on IVA (see **Renewal Criteria**)	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is this the first time the patient is requesting a renewal (after 90 days of initial approval)?	**Yes:** Go to #2	**No:** Go to #4
2. If prescription is for ivacaftor: Does the patient have a documented physiological response to therapy and evidence of adherence after 30 days of treatment, as defined by a sweat chloride test that has decreased by at least 20 mmol/L from baseline?	**Yes:** Go to #7	**No:** Go to #3 Consider patient's adherence to therapy and repeat test in 2 weeks to 45 days to allow for variability in test. If sodium chloride has still not decreased by 20 mmol/L, deny therapy for medical appropriateness
3. If the prescription is for lumacaftor/ivacaftor or tezacaftor/ivacaftor: Is there evidence of adherence and tolerance to therapy through pharmacy claims/refill history and provider assessment?	**Yes:** Go to #7	**No:** Pass to RPh; Deny (medical appropriateness)

Renewal Criteria		
4. Does the patient have documented response to therapy as defined as below : For patients age ≥6 years: • An improvement or lack of decline in lung function as measured by the FEV1 when the patient is clinically stable; OR • A reduction in the incidence of pulmonary exacerbations; OR • A significant improvement in BMI by 10% from baseline? For patients age 2-5 years (cannot complete lung function tests) • Significant improvement in BMI by 10% from baseline; OR • Improvement in exacerbation frequency or severity; OR • Sweat chloride test has decreased from baseline by 20 mmol/L from baseline?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Has the patient been compliant with therapy, as determined by refill claims history?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Have liver function tests been appropriately monitored? What are the most recent liver function tests (AST, ALT, and bilirubin)? Note: Monitoring LFTs is recommended every 3 months for the first year, followed by once a year.	Document. Go to #7 Note: Therapy should be interrupted in patients with AST or ALT >5x the upper limit of normal (ULN), or ALT or AST >3x ULN with bilirubin >2x ULN.	

Renewal Criteria		
7. Is the CFTR modulator dosed appropriately based on age, weight, and co-administered drugs (see dosing and administration below)?	**Yes:** Approve for additional 3 months (total of 6 months since start of therapy)	**No:** Pass to RPh. Deny; medical appropriateness

Dosage and Administration:

Ivacaftor:

- Adults and pediatrics age ≥6 years: 150 mg orally every 12 hours with fat-containing foods
- Children age 2 to <6 years:
  - < 14 kg: 50 mg packet every 12 hours
  - ≥ 14 kg: 75 mg packet every 12 hours
- Hepatic Impairment
  - Moderate Impairment (Child-Pugh class B):
    - Age ≥6 years: one 150 mg tablet once daily
    - Age 2 to < 6 years with body weight < 14 kg: 50 mg packet once daily; with body weight ≥ 14 kg : 75 mg packet of granules once daily
  - Severe impairment (Child-Pugh class C): Use with caution at a dose of 1 tablet or 1 packet of oral granules once daily or less frequently.
- Dose adjustment with concomitant medications:

Table 1. Examples of CYP3A4 inhibitors and inducers.

Drug co-administered with IVA	Co-administered drug category	Recommended dosage adjustment for IVA
Ketoconazole Itraconazole Posaconazole Voriconazole Clarithromycin Telithromycin	CYP3A4 strong inhibitors	Reduce IVA dose to 1 tablet or 1 packet of oral granules **twice weekly** (one-seventh of normal initial dose)
Fluconazole Erythromycin Clofazimine	CYP3A4 moderate inhibitors	Reduce IVA dose to 1 tablet or 1 packet of oral granules **once daily** (half of normal dose)
Rifampin	CYP3A4 strong inducers	Concurrent use is **NOT** recommended

Rifabutin Phenobarbital Phenytoin Carbamazepine St. John's wort Grapefruit Juice		

Lumacaftor/ivacaftor

- Adults and pediatrics age ≥12 years: 2 tablets (LUM 200 mg/IVA 125 mg) every 12 hours
- Pediatric patients age 6 through 11 years: 2 tablets (LUM 100mg/IVA 125 mg) every 12 hours
- Hepatic impairment
    - Moderate impairment (Child-Pugh class B):
        - 2 tablets in the morning and 1 tablet in the evening
    - Severe impairment (Child-Pugh class C): Use with caution at a dose of 1 tablet twice daily, or less, after weighing the risks and benefits of treatment.
- Dose adjustment with concomitant medications:
    - When initiating therapy in patients taking strong CYP3A inhibitors (see table above), reduce dose to 1 tablet daily for the first week of treatment. Following this period, continue with the recommended daily dose.

Tezacaftor/ivacaftor:

- Adults and pediatrics age ≥12 years: 1 tablet (TEZ 100 mg/IVA 150 mg) in the morning and IVA 150 mg in the evening
- Hepatic impairment
    - Moderate impairment (Child-Pugh class B):
        - 1 tablet (TEZ 100 mg/IVA 150 mg) in the morning. The evening IVA dose should not be administered.
    - Severe impairment (Child-Pugh class C):
        - 1 tablet (TEZ 100 mg/IVA 150 mg) in the morning (or less frequently). The evening IVA dose should not be administered.
- Dose adjustment with concomitant medications:
    - When initiating therapy in patients taking moderate CYP3A inhibitors (see table above), reduce dose to:
        - On day 1, TEZ 100/IVA 150 once daily in the morning, and on day 2, IVA 150 mg once daily in the morning; continue this dosing schedule.
    - When initiating therapy in patients taking strong CYP3A4 inhibitors (See table above), reduce dose to:
        - TEZ 100 mg/IVA 150 mg twice a week, administered 3 to 4 days apart. The evening dose of IVA 150 mg should not be administered.

1. Orkambi Prescribing Information. Prescribing Information. Vertex Pharmaceuticals. Boston, MA 02210. August 2018. https://pi.vrtx.com/files/uspi_lumacaftor_ivacaftor.pdf.
2. Kalydeco Prescribing Information. Vertex Pharmaceuticals. August 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/203188s028,207925s007lbl.pdf.
3. Rosenfeld M, Wainwright CE, Higgins M, et al. Ivacaftor treatment of cystic fibrosis in children aged 12 to <24 months and with a CFTR gating mutation (ARRIVAL): a phase 3 single-arm study. *The Lancet Respiratory medicine.* 2018;6(7):545-553.
4. Rowe SM, Daines C, Ringshausen FC, et al. Tezacaftor-Ivacaftor in Residual-Function Heterozygotes with Cystic Fibrosis. *The New England journal of medicine.* 2017;377(21):2024-2035.

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Prior Authorization Update: Botulinum Toxins

Background:
The Oregon Health Authority (OHA) Health Evidence Review Commission (HERC) recommended amending Guideline Note 42, Chemodenervation for Chronic Migraine, of the Prioritized List of Health Services at the August 2018 meeting.[1] The following recommended changes will go into effect on October 1, 2018:

- Removal of calcium channel blockers from the recommended classes of pharmacological prophylaxis therapies[1]
- Addition of criteria which requires that the patient's condition has been appropriately managed for medication overuse[1]

With these changes, the updated Guideline Note will read as follows:

> GUIDELINE NOTE 42, CHEMODENERVATION FOR CHRONIC MIGRAINE
> *Line 409*
> Chemodenervation for treatment of chronic migraine (CPT 64615) is included on this line for prophylactic treatment of adults who meet all of the following criteria:
>
> A) have chronic migraine defined as headaches on at least 15 days per month of which at least 8 days are with migraine
> B) has not responded to or have contraindications to at least three prior pharmacological prophylaxis therapies (beta-blocker, anticonvulsant, or tricyclic antidepressant)
> C) their condition has been appropriately managed for medication overuse
> D) treatment is administered in consultation with a neurologist or headache specialist.
>
> Treatment is limited to two injections given 3 months apart. Additional treatment requires documented positive response to therapy. Positive response to therapy is defined as a reduction of at least 7 headache days per month compared to baseline headache frequency.

Purpose of the Prior Authorization Update:
The purpose of this prior authorization (PA) update is to align the botulinum toxins PA criteria with the updated Guideline Note.

Recommendations:

- Update PA criteria to reflect current guidelines in the OHA Prioritized List of Health Services as outlined in **Appendix 1**.

References:

1. Health Evidence Review Commission's Value-based Benefits Subcommittee Meeting Materials. Oregon Health Authority. August 9, 2018. https://www.oregon.gov/oha/HPA/CSI-HERC/MeetingDocuments/VBBS%20Meeting%20Materials%208-9-2018.pdf. Accessed August 21, 2018.

Botulinum Toxins

Goal(s):
- Approve botulinum toxins for funded OHP conditions supported by evidence of benefit.
- Require positive response to therapy for use in chronic migraine headaches or overactive bladder.

Length of Authorization:
- From 90 days to 12 months

Requires PA:
- Use of botulinum toxins (billed as a physician administered or pharmacy claim) without associated dystonia or neurological disease diagnosis in last 12 months.

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

Approval Criteria		
1. Is this a request for renewal of a previously approved prior authorization for management of migraine headache or detrusor over-activity (e.g., overactive bladder)?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code	

Approval Criteria		
3. Is botulinum toxin treatment for any of the following? a. Upper or lower limb spasticity (G24.02, G24.1, G35, G36.0, I69.03- I69.06 and categories G71, and G80-G83); b. Strabismus due to a neurological disorder (H50.89); c. Blepharospasm (G24.5); d. Spasmodic torticollis (G24.3); e. Torsion dystonia (G24.9); or f. Achalasia (K22.0).	**Yes:** Approve for up to 12 months	**No:** Go to #4
4. Is botulinum toxin treatment for chronic migraine, with ≥15 headache days per month, of which ≥8 days are with migraine?	**Yes:** Go to #5	**No:** Go to #8~~7~~
5. Is the botulinum toxin administered by, or in consultation with, a neurologist or headache specialist?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Has the patient had an inadequate response, or has contraindications, to ~~≥1 drugs from~~ at least 3 pharmacological prophylaxis therapies~~of the following drug classes~~? • Beta-blockers~~:~~ (i.e., propranolol; metoprolol; atenolol; nadolol; or timolol) • Tricyclic antidepressants~~:~~ (i.e., nortriptyline or amitriptyline) • Anticonvulsants~~:~~ (i.e., divalproex sodium/valproic acid; carbamazepine; topiramate; or gabapentin) • ~~Calcium channel blockers (diltiazem; verapamil; or nimodipine)~~	**Yes:** Go to #7 Baseline headaches/month: _____. ~~Approve no more than 2 injections given ≥3 months apart.~~ ~~Additional treatment requires documented positive response to therapy from baseline (see Renewal Criteria).~~	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of preferred alternatives at www.orpdl.org/drugs/

Approval Criteria		
7. Do chart notes indicate headaches are due to medication overuse?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve no more than 2 injections given ≥3 months apart. Additional treatment requires documented positive response to therapy from baseline (see Renewal Criteria).
~~7.~~8. Is botulinum toxin treatment for idiopathic or neurogenic detrusor over-activity (ICD10-CM N32.81)?	**Yes:** Go to #~~9~~8	**No:** Pass to RPh. Go to #10~~9~~
~~8.~~9. Has the patient had an inadequate response to, or is intolerant of, ≥2 incontinence anti-muscarinic drugs (e.g., fesoterodine, oxybutynin, solifenacin, darifenacin, tolterodine, or trospium)?	**Yes:** • Baseline urine frequency/day: _____. • Baseline urine incontinence episodes/day: _____. Approve for up to 90 days. Additional treatment requires documented positive response to therapy from baseline (see Renewal Criteria).	**No:** Pass to RPh. Deny; medical appropriateness.

~~9.~~10. RPh only: Medical literature with evidence for use in funded conditions must be submitted and determined to be appropriate for use before approval is granted.

Deny for the following conditions; not funded by the OHP
Axillary hyperhidrosis and palmar hyperhidrosis (ICD-10 L74.52, R61) Neurologic conditions with none or minimally effective treatment or treatment not necessary (G244; G2589; G2581; G2589; G259); Facial nerve disorders (G510-G519); Spastic dysphonia (J387); Anal fissure (K602); Disorders of sweat glands (e.g., focal hyperhidrosis) (L301; L740-L759; R61); Other disorders of cervical region (M436; M4802; M530; M531; M5382; M5402; M5412; M542; M6788); Acute and chronic disorders of the spine without neurologic impairment (M546; M545; M4327; M4328; M532X7; M532X8; M533; M438X9; M539; M5408; M545; M5430; M5414-M5417; M5489; M549); Disorders of soft tissue (M5410; M609; M790-M792; M797); Headaches (G44209; G44009; G44019; G44029; G44039; G44049; G44059; G44099; G44209; G44219; G44221; G44229; G44309; G44319; G44329; G4441; G4451-G4453; G4459; G4481-G4489; G441; R51); Gastroparesis (K3184) Lateral epicondylitis (tennis elbow)) (M7710-M7712)
Deny for medical appropriateness because evidence of benefit is insufficient

Dysphagia (R130; R1310-R1319);
Other extrapyramidal disease and abnormal movement disorders (G10; G230-GG238; G2401; G244; G250-G26);
Other disorders of binocular eye movements (e.g., esotropia, exotropia, mechanical strabismus, etc.) (H4900-H518);
Tics (F950-F952; F959);
Laryngeal spasm (J385);
Spinal stenosis in cervical region or brachial neuritis or radiculitis NOS (M4802; M5412-M5413);
Spasm of muscle in absence of neurological diagnoses (M6240-M62838);
Contracture of tendon (sheath) in absence of neurological diagnoses (M6240; M62838);
Amyotrophic sclerosis (G1221);
Clinically significant spinal deformity or disorders of spine with neurological impairment (M4800; M4804; M4806; M4808; M5414-M5417);
Essential tremor (G25.0)
Hemifacial spasm (G513)
Occupational dystonias (e.g., “Writer’s cramp”) (G248, G249)
Hyperplasia of the prostate (N400-403; N4283)
Conditions of the back and spine for the treatment of conditions on lines 346 and 527, including cervical, thoracic, lumbar and sacral conditions. See Guideline Note 37.

Renewal Criteria		
1. Is this a request for renewal of a previously approved prior authorization for management of migraine headache?	**Yes:** Go to #2	**No:** Go to #3
2. Is there documentation of a reduction of ≥7 headache days per month compared to baseline headache frequency?	**Yes:** Approve no more than 2 injections given ≥3 months apart. Baseline:____ headaches/month Current:____ headaches/month	**No:** Pass to RPh. Deny; medical appropriateness
3. Is this a request for renewal of a previously approved prior authorization for management of idiopathic or neurogenic detrusor over-activity?	**Yes:** Go to #4	**No:** Go to Approval Criteria
4. Is there a reduction of urinary frequency of ≥8 episodes per day or urinary incontinence of ≥2 episodes per day compared to baseline frequency?	**Yes:** Approve for up to 12 months • Baseline:____ urine frequency/day • Current:____ urine frequency/day -or- • Baseline:____ urine incontinence episodes/day • Current:____ urine incontinence episodes/day	**No:** Pass to RPh. Deny; medical appropriateness

P&T / DUR Review: *9/18 (JP); 5/18; 11/15; 9/14; 7/14*
Implementation: *TBD; 7/1/18; 10/13/16; 1/1/16*