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

Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, January 26, 2017 1:00 - 5:00 PM
Barbara Roberts Human Services Building, HSB 137 A-D
500 Summer St. NE
Salem, OR 97301

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. Election of Chair & Vice Chair	R. Citron (OSU)
	D. Approval of Agenda and Minutes	Chair
	E. Department Update	D. Weston (OHA)
	II. DUR OLD BUSINESS	
1:15 PM	A. Buprenorphine and Vivitrol® (naltrexone ER inj.) Drug Policies 1. Prior Authorization Criteria Clarification 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	A. Gibler (OSU)
1:30 PM	B. Oral Multiple Sclerosis Drug Policy 1. Prior Authorization Criteria Clarification 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	A. Gibler (OSU)
	III. PREFERRED DRUG LIST NEW BUSINESS	
1:40 PM	A. Gout Drugs Class Update 1. Class Update/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	K. Sentena (OSU)

2:00 PM	B. Conventional Antiemetics Class Review 1. Class Review/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	D. Moretz (OSU)
2:10 PM	C. Hormone Replacement Therapy Class Update 1. Class Update/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	S. Servid (OSU)
2:30 PM	D. Antidiarrheals Class Review 1. Class Review 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	D. Moretz (OSU)
2:45 PM	E. Vitamin D Analogs Class Review 1. Class Review 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	K. Sentena (OSU)
3:00 PM	BREAK	
3:20 PM	F. Ocaliva® (obeticholic acid) New Drug Evaluation 1. New Drug Evaluation/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	S. Servid (OSU)
3:35 PM	G. Adlyxin® (lixisenatide) New Drug Evaluation 1. New Drug Evaluation/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	K. Sentena (OSU)
3:50 PM	H. Zinbryta™ (daclizumab) New Drug Evaluation 1. New Drug Evaluation/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	D. Moretz (OSU)
As time allows	I. Nuplazid™ (pimavanserin) New Drug Evaluation 1. New Drug Evaluation/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	S. Servid (OSU)
As time allows	J. Xiidra™ (lifitegrast) New Drug Evaluation 1. New Drug Evaluation 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	K. Sentena (OSU)

4:00 PM IV. EXECUTIVE SESSION

4:50 PM V. RECONVENE for PUBLIC RECOMMENDATIONS

5:00 PM VI. ADJOURN

Drug Use Research & Management Program
OHA Health Systems Division
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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 2017
Caryn Mickelson, Pharm.D.	Pharmacist	Pharmacy Director	Coos Bay	December 2017
Tracy Klein, Ph.D., F.N.P.	Public	Nurse Practitioner	Portland	December 2017
James Slater, Pharm.D.	Pharmacist	Pharmacy Director	Beaverton	December 2017
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
Kelley Burnett, D.O.	Physician	Pediatric Medical Director	Grants Pass	December 2019

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, November 17, 2016 1:00-5:00 PM
Hewlett-Packard Building
Salem, OR 97302

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: Bill Origer, MD; Tracy Klein, PhD, FNP; Rich Clark, MD, MPH; Walter Hardin, D.O., MBA; Cathy Zehrung, RPh; Phil Levine, PhD

Members Present by Phone: James Slater, PharmD

Staff Present: Andrew Gibler, PharmD; Megan Herink PharmD, BCPS; Richard Holsapple, RPh; Roger Citron, RPh; Ted Williams, PharmD, BCPS; Dee Weston; Dave Engen, PharmD, CGP; Sarah Servid, PharmD; Kim Wentz, MD; Deanna Moretz, PharmD, BCPS; Lindsay Newton; Emily Church; Jim Rickards, MD

Staff Present by Phone: Kathy Sentena, PharmD

Audience: Luis Velasquez/Vertex; Venus Holder/Lilly; Tony Hasan/Lilly; *Lisa Allen/Vertex; *Anthony Wheeler/Lilly; David Barhoum/Genentech; Jan Leach/Genentech; Lindsay Bahr/Mallinckrodt; Becky Hanson/Quintiles IMS; Melissa Snider/Biomarin; Kerry Bonilla/AstraZeneca; Risa Reuscher/Amgen; *Sylvia Churchill/Amgen; *Margaret Olmon/Abbvie; *Lynda Finch/Biogen; Diann Matthews/Biogen; Jennifer Shidler/SanofiGenayone; Stephanie Roberts/Acorda; Jeana Colabianchi/Sunovion; Rick Frees/Vertex; Lisa Boyle/WVP Health Authority; Matt Medina/Purdue; Brianna Mendoza; *Kari Rose; *Talon Hyatt; *Kim Osmus/Katie's Kause for CF; *Mike Powers/OHSU CF Center; Paul Nielsen/Alkermes; Deron Grothe/Teva;

(*) Provided verbal testimony

Written testimony provided: Sue Landgraf/Cystic Fibrosis Research Inc.; Bruce Marshall & Lisa Feng/Cystic Fibrosis Foundation

I. CALL TO ORDER

A. The meeting was called to order at approximately 1:05 pm. Introductions were made by Committee members and staff.

B. Mr. Citron reported there were no new conflicts of interest to declare.

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

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

D. Department updates for OHA presented by Dr. Rickards and Ms. Weston.

II. DUR ACTIVITIES

A. CMS Annual Report – presented by Ms. Weston
B. Quarterly Utilization Report (pages 8-12) – presented by Mr. Citron
C. ProDUR Report (pages 13-15) – presented by Mr. Holsapple
D. RetroDUR Report (pages 16-20) – presented by Dr. Williams
E. Oregon State Drug Reviews (pages 21-30) – presented by Dr. Sentena
   1. Who Benefits from Calcium and Vitamin D Supplementation?
   2. Pharmacist Prescribed Contraceptives
   3. Vaccine Update 2016
   4. Endocrine Therapy for Breast Cancer

Dr. Clark voiced his concern with reporting statistical significance vs. clinical significance in the newsletters. Dr. Gibler highlighted the importance of real outcomes such as mortality, fractures, etc. and recommended we will include NNT when possible. Dr. Clark seemed satisfied with the recommendation.

F. Dose Consolidation Lettering Proposal (pages 31-42) – presented by Dr. Williams

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

III. PREFERRED DRUG LIST NEW BUSINESS

A. Synagis ® (palivizumab) Drug Policy (pages 43 - 47)
Dr. Engen presented the class update and following recommendation:

1. Update current clinical prior authorization criteria to require that the patient's parent/caregiver and prescriber comply with all case management services, including obtaining current patient weight throughout approved treatment period.

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

B. Procysbi ® (cysteamine delayed-release) Drug Policy (pages 48 - 51)
Dr. Moretz presented the class update and the following recommendation:

1. No changes to the current clinical prior authorization criteria are recommended.

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

C. H.P. Acthar Gel® (repository corticotropin inj) Drug Policy (pages 52 - 56)
Dr. Moretz presented the scan and following recommendation:

1. No changes to the current clinical prior authorization criteria are recommended.

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

D. Oral Cystic Fibrosis Modulators Class Update (pages 57 - 72)
Dr. Herink presented the class update and the following recommendations:

1. No changes to the PDL are recommended.
2. Continue to require clinical prior authorization for approval in appropriate patients and amend criteria to reflect FDA approval for use of Orkambi (lumacaftor/ivacaftor) in children ages 6 through 11 years. If clinical PA criteria are fulfilled, refer claims for this age group to the Medical Director for approval.

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

E. Opioid Analgesics Class Update (pages 73-108)
Dr. Gibler presented the following class update and recommendations:

1. Review comparative short-acting opioid costs in the executive session to inform PDL status of this class.
2. Maintain non-preferred status for Troxyca ER (oxycodone/naltrexone) extended-release capsules.
3. Approve the proposed clinical prior authorization criteria for short- and long-acting opioid analgesics:
    a. Patients with a terminal diagnosis or cancer diagnosis are exempt from prior authorization.
    b. All non-preferred short-acting opioids and preferred short-acting opioids prescribed for more than 7 days are subject to prior authorization.
    c. All long-acting opioid analgesics are subject to prior authorization.
    d. Update quantity limits for new long-acting opioid approvals.
4. Oregon Health Authority to work with the Pharmacy Benefits Manager (HPE) on timing of implementation of these new drug policies. This will need to include an educational component.

The Committee recommended modify question #8 of the proposed short-acting opioid clinical PA criteria to remove restriction that opioid analgesics be prescribed by a single prescriber or prescribing practice. Instead request prescriber simply review the scheduled substances the patient has been recently prescribed. For long-acting opioids, the

Committee recommended making clerical or visual changes to Table 1 of the proposed PA criteria to separate and highlight methadone as being a uniquely different opioid than the other agents.

The Committee debated lowering the maximum prescribed amount from 90 daily MME to 50 daily MME. Consensus could not be reached so a vote was taken and Dr. Clark voted for lowering to 50 daily MME, while the majority voted to keep it at 90 daily MME.

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

F. Multiple Sclerosis Drug Class Update (pages 109-133)
Dr. Moretz presented the class update along with the following recommendations:

1. No changes recommended to the PDL based on evidence from the DERP report. Evaluate comparative drug costs in the executive session.
2. Revise clinical prior authorization criteria to require assessment of lymphocyte counts before initiating therapy with Tecfidera (dimethyl fumarate).

The Committee recommended modifying question #9 of the clinical PA criteria to also require confirmation of a negative pregnancy test prior to initiation of teriflunomide.

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

G. Taltz (ixekizumab) New Drug Evaluation (pages 134-151)
Dr. Gibler presented the class update along with the following recommendations:

1. Incorporate Taltz (ixekizumab) into current prior authorization criteria for Biologics. No changes to the clinical criteria recommended.
2. Evaluate comparative drug costs in the executive session to determine PDL status for Taltz (ixekizumab).

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

H. Non-statin Lipid-lowering Agents Class Update (pages 152-182)
Dr. Moretz presented the class update along with the following recommendations:

1. No changes to the PDL recommended based on updated evidence. Review comparative drug costs in the executive session.
2. Revise current clinical prior authorization criteria for omega-3 fatty acids to remove requirement of failure or contraindication to niacin therapy as condition for approval.
3. No changes to clinical prior authorization criteria for PCSK9 Inhibitors, mipomersen or lomitapide recommended.

The Committee recommended modifying the goal for the PA of omega-3 fatty acids to state it is to restrict use of omega-3 fatty acids to patients at increased risk for pancreatitis.

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

V. EXECUTIVE SESSION

VI. RECONVENE FOR PUBLIC RECOMMENDATIONS * After executive session

A. Opioid Analgesics Class Update (pages 73-108)
*__ACTION:__ Recommend no changes to the PMPDP.
Motion, 2nd, All in Favor. Approved.

B. Multiple Sclerosis Drug Class Update (pages 109-133)
*__ACTION:__ Make Glatopa non-preferred, request pharmacies dispense Copaxone brand.
Motion, 2nd, All in Favor. Approved

C. Taltz (ixekizumab) New Drug Evaluation (pages 134-151)
*__ACTION:__ Maintain TALTZ PDL=N. Recommend no changes to the PMPDP.
Motion, 2nd, All in Favor. Approved

D. Non-statin Lipid-lowering Agents Class Update (pages 152-182)
*__ACTION:__ Recommend no changes to the PMPDP.
Motion, 2nd, All in Favor. Approved

VII. ADJOURN

Buprenorphine and Buprenorphine/Naloxone

Goals:

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

Length of Authorization:

Up to 6 months

Requires PA:

- Buprenorphine sublingual tablets
- Suboxone® and generics (buprenorphine/naloxone) film and sublingual tablets that exceed an average daily dose of 24 mg per day of buprenorphine
- Bunavail® (buprenorphine/naloxone buccal film)
- Zubsolv® (buprenorphine/naloxone sublingual tablets)
- Probuphine® (buprenorphine subdermal implants)

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 prescription for opioid use disorder (opioid dependence or addiction)?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the patient part of a comprehensive treatment program for substance abuse that includes psychosocial support system(s)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness. Buprenorphine therapy must be part of a comprehensive treatment program that includes psychosocial support.

Approval Criteria		
4. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com) and has the prescriber verified at least once in the past 6 months that the patient has not been prescribed any opioid analgesics from other prescribers?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the requested medication a preferred agent?	**Yes:** Go to #7	**No:** Go to #6
6. Will the prescriber switch to a preferred product? Note: Preferred products are reviewed for comparative safety and efficacy by the Oregon Pharmacy and Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #7
7. Is the request for the buprenorphine implant system (Probuphine)?	**Yes:** Go to #8	**No:** Go to #9
8. Has the patient been *clinically stable* on 8 mg daily or less of Suboxone or Subutex (or equivalent, see Table 1) for at least 6 months? Note: see Table 1 for definition of clinical stability and for equivalent dosing of other buprenorphine products.	**Yes:** if <u>all</u> criteria in Table 1 met, approve 4 implants for 6 months	**No:** Pass to RPh. Deny; medical appropriateness
9. Is the prescription for a transmucosal formulation of buprenorphine (film, tablet) with an average daily dose of more than 24 mg (e.g., >24 mg/day or >48 mg every other day)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #10
10. Is the prescribed product a buprenorphine monotherapy product (i.e., without naloxone)	**Yes:** Go to #11	**No:** Go to #13
11. Is the patient pregnant or a female actively trying to conceive?	**Yes:** Go to #13	**No:** Go to #12

Approval Criteria		
12. Does the patient have a contraindication or intolerance to buprenorphine/naloxone combination products that prevents successful management of opioid use disorder?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness
~~13. What is the patients' pharmacy-of-choice?~~ ~~Document pharmacy name and NPI or address in PA record. Lock patient into their pharmacy-of-choice for 6 months.~~	~~Inform prescriber patient will be locked into a single pharmacy for all prescriptions. Go to #14~~	
~~14.~~13. What is the expected length of treatment?	Document length of therapy: _____ Approve for anticipated length of treatment or 6 months, whichever is shorter.	

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

PROBUPHINE implants are only for use in patients who meet ALL of the following criteria:

• Patients should not be tapered to a lower dose for the sole purpose of transitioning to PROBUPHINE
• Stable transmucosal buprenorphine dose (of 8 mg per day or less of a sublingual Subutex or Suboxone sublingual tablet or its transmucosal buprenorphine product equivalent) for 3 months or longer without any need for supplemental dosing or adjustments:
  ○ Examples of acceptable daily doses of transmucosal buprenorphine include:
  ▪ Subutex (buprenorphine) sublingual tablet (generic equivalent) 8 mg or less
  ▪ Suboxone (buprenorphine and naloxone) sublingual tablet (generic equivalent) 8 mg/2 mg or less
  ▪ Bunavail (buprenorphine and naloxone) buccal film 4.2 mg/0.7 mg or less
  ▪ Zubsolv (buprenorphine and naloxone) sublingual tablets 5.7 mg/1.4 mg or less

Consider the following factors in determining clinical stability and suitability for PROBUPHINE treatment: • no reported illicit opioid use • low to no desire/need to use illicit opioids • no reports of significant withdrawal symptoms • stable living environment • participation in a structured activity/job that contributes to the community • consistent participation in recommended cognitive behavioral therapy/peer support program • stability of living environment • participation in a structured activity/job
Reference: PROBUPHINE (buprenorphine implant for subdermal administration) [Prescribing Information]. Princeton, MJ: Braeburn Pharmaceuticals, Inc., May 2016.

Naltrexone Extended Release Inj. (Vivitrol®)

Goal(s):

- Promote safe and cost effective therapy for the treatment of alcohol and opioid dependence.

Length of Authorization:

Up to 6 months

Requires PA:

- ~~Vivitrol® (naltrexone extended-release inj.)~~ NO PA REQUIRED

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. Will the prescriber switch to a preferred product? Note: Preferred products are reviewed for comparative safety and efficacy by the Oregon Pharmacy and Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #3
3. Does the patient have a diagnosis of alcohol dependence (DSM-IV-TR) or alcohol use disorder (DSM-V)?	**Yes:** Go to #4	**No:** Go to #5
4. Has the requesting prescriber provided documentation and/or confirmation of abstinence from alcohol as assessed by the provider or by objective testing?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness. Patients must have demonstrated alcohol abstinence prior to administration.
5. Does the patient have a diagnosis of opioid dependence (DSM-IV-TR) or opioid use disorder (DSM-V)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
6. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com) and has the prescriber verified at least once in the past 6 months that the patient has not been prescribed any opioid analgesics from other prescribers?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Is the patient physiologically free of opioid dependence for ≥7 days, as confirmed by: a. Negative urine drug screen for opioids (including heroin) and their metabolites; and b. Negative naloxone challenge test (0.8 to 1.6 mg of IM/IV naloxone; or alternatively, 50 mg or oral naloxone with no subsequent withdrawal symptoms)?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness.
8. Has the patient tried and failed first-line oral opioid agonists (buprenorphine/naloxone or methadone) if for the treatment of opioid dependency; or is the patient unable to take oral therapy or requires injectable therapy due to poor adherence?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness.
9. Is the patient part of a comprehensive treatment program for substance abuse that includes psychosocial support system(s)?	**Yes:** Approve one 380 mg injection every 4 weeks for up to 6 months.	**No:** Pass to RPh. Deny; medical appropriateness. Naltrexone extended-release injection therapy must be part of a comprehensive treatment program that includes psychosocial support.

P&T Review: *1/17 (AG); 9/16; 1/15; 5/14; 11/13*
Implementation: *1/1/14*

Oral Multiple Sclerosis Drugs

Goal(s):
- Promote safe and effective use of oral disease-modifying multiple sclerosis drugs
- Promote use of preferred multiple sclerosis drugs.

Length of Authorization:
- Up to 12 months

Requires PA:
- Fingolimod
- Teriflunomide
- Dimethyl Fumarate

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Does the patient have a diagnosis of relapsing remitting~~primary or secondary progressive~~ multiple sclerosis?	**Yes:** Go to #3~~Pass to RPh. Deny; not funded by the OHP. See Guideline Note 95 in the Prioritized List of Health Services.~~	**No:** Pass to RPh. Deny; not funded by the OHP. See Guideline Note 95 in the Prioritized List of Health Services.~~Go to #3~~
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics Committee and do not require PA.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #4
4. Has the patient failed or cannot tolerate a trial of interferon beta 1a or interferon beta 1b, and glatiramer?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness.
5. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is the patient on concurrent treatment with a disease modifying drug (i.e. interferon beta 1B, glatiramer acetate, interferon beta 1A, natalizumab, mitoxantrone)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #7

Approval Criteria		
7. Is the prescription for teriflunomide?	**Yes:** Go to #8	**No:** Go to #10
8. Is the patient of childbearing potential?	**Yes:** Go to #9	**No:** Approve for up to 1 year.
9. Is the patient currently on a documented use of reliable contraception and is there documentation of a negative pregnancy test prior to initiation of teriflunomide?	**Yes:** Approve for up to 1 year.	**No:** Pass to RPh. Deny; medical appropriateness.
10. Is the prescription fingolimod?	**Yes:** Go to #11	**No:** Go to #14
11. Does the patient have evidence of macular edema?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #12
12. Does the patient have preexisting cardiac disease, risk factors for bradycardia, or is on anti-arrhythmic, beta-blockers, or calcium channel blockers?	**Yes:** Go to #13	**No:** Approve up to 1 year.
13. Has the patient had a cardiology consultation before initiation (see clinical notes)?	**Yes:** Approve up to 1 year.	**No:** Pass to RPh. Deny; medical appropriateness.
14. Is the prescription for dimethyl fumarate?	**Yes:** Go to # 15	**No:** Pass to RPh. Deny; medical appropriateness.
15. Does patient have a baseline CBC with lymphocyte count greater than 500/µL?	**Yes:** Approve for up to 1 year	**No:** Pass to RPh. Deny; medical appropriateness.

Fingolimod Clinical Notes:

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

Teriflunomide Clinical Notes:

- Before starting teriflunomide, screen patients for latent tuberculosis infection with a TB skin test, exclude pregnancy, confirm use of reliable contraception in women of childbearing potential, check blood pressure, and obtain a complete blood cell count within the 6 months prior to starting therapy. Instruct patients to report symptoms of infection and obtain serum transaminase and bilirubin levels within the 6 months prior to starting therapy.
- After starting feriflunomide, monitor ALT levels at least monthly for 6 months. Consider additional ALT monitoring when feriflunomide is given with other potentially hepatotoxic drugs. Consider stopping feriflunomide if serum

transaminase levels increase (>3-times the ULN). Monitor serum transaminase and bilirubin particularly in patients who develop symptoms suggestive of hepatic dysfunction. Discontinue teriflunomide and start accelerated elimination in those with suspected teriflunomide-induced liver injury and monitor liver tests weekly until normalized. Check blood pressure periodically and manage hypertension. Check serum potassium level in teriflunomide-treated patients with hyperkalemia symptoms or acute renal failure. Monitor for signs and symptoms of infection.

- Monitor for hematologic toxicity when switching from teriflunomide to another agent with a known potential for hematologic suppression because systemic exposure to both agents will overlap.

Dimethyl Fumarate Clinical Notes:

- Dimethyl fumarate may decrease a patient's white blood cell count. In the clinical trials the mean lymphocyte counts decreased by approximately 30% during the first year of treatment with dimethyl fumarate and then remained stable. The incidence of infections (60% vs. 58%) and serious infections (2% vs. 2%) was similar in patients treated with dimethyl fumurate or placebo, respectively. There was no increased incidence of serious infections observed in patients with lymphocyte counts <0.8 $x10^3$ cells/mm^3. A transient increase in mean eosinophil counts was seen during the first 2 months of therapy.
- Dimethyl fumarate should be held if the WBC falls below 2 $x10^3$ cells/mm^3 or the lymphocyte count is below 0.5 $x10^3$ cells/mm^3 and permanently discontinued if the WBC did not increase to over 2 $x10^3$ cells/mm^3 or lymphocyte count increased to over 0.5 $x10^3$ cells/mm^3 after 4 weeks of withholding therapy.
- Patients should have a CBC with differential monitored on a quarterly basis

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

Drug Use Research & Management Program
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Salem, Oregon 97301-1079
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Class Update: Drugs for Gout

Date of Review: January 2017 **Date of Last Review:** May 2015 (lesinurad, July 2016)

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

Purpose for Class Update:
The Oregon Drug Use Review / Pharmacy and Therapeutics Committee requested specific clinical criteria to guide prescribers to appropriate step therapy for management of hyperuricemia and gout flares.

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Research Questions:

1. In adult patients with a history of gout, is there new evidence for differences in efficacy or effectiveness between drug therapies used for prevention and treatment of acute gout attack?
2. Does current evidence suggest appropriate pharmacological step therapy for the prevention of acute gout attacks in adult patients with recurrent gout attacks?
3. In adult patients with a history of gout, is there new evidence for differences in harms between drug therapies used for prevention and treatment of acute gout attacks?
4. Are there subpopulations based on co-morbid conditions (i.e., renal insufficiency, peptic ulcer disease) or gout history (i.e., acute versus chronic) in which one drug may be more effective or associated with less harm than other drugs used for prevention of gout flares?

Conclusions:

- Drugs for gout were reviewed in May of 2015, as well as a new drug review in July of this year. Since the last class update there has been one high quality systematic review on the management of gout from the Agency for Healthcare Research and Quality (AHRQ), one systematic review on the use of allopurinol with urate lowering therapy (ULT) and 2 new evidence-based guidelines, one from the European League Against Rheumatism (EULAR) and one from the American College of Physicians (ACP).[1, 2, 3, 4]
- Evidence on drug therapies was insufficient for outcomes of joint tenderness, swelling, activities of daily living and patient global assessment.
- Efficacy outcomes studied were the following: pain, serum urate levels, and incidence of gout attacks.
    - There is high strength of evidence to support the use of NSAIDs, colchicine and systemic corticosteroids for pain relief in patients with acute gout.[1,3,4]
    - Serum urate levels were found to be reduced with allopurinol and febuxostat based on high strength of evidence.[1]
    - Moderate evidence found low dose colchicine to offer similar pain relief with less adverse events as high-dose colchicine,[1] therefore, low-dose is recommended when using colchicine for the treatment of acute gout.[4]

- Use of prophylactic therapy with low-dose colchicine or low dose NSAIDs reduces the risk of an acute gout attack in patients starting on ULT based on high strength evidence.[1]
- There is high quality evidence for the use of allopurinol first line for those patients who are candidates for ULT therapy.[3]
- There is high quality evidence that low dose colchicine or low dose NSAIDs at the start of ULT initiation, reduces the risk of an acute gout attack by a similar amount.[1,4] EULAR guidelines recommend flare prophylaxis for the first 6 months with colchicine, with NSAIDs as an alternative option.[3]
- Combinations of allopurinol and uricosurics are recommended for patients requiring additional therapy to obtain target serum urate levels.[3]
- There was low level evidence that targeting a specific urate level reduces the risk of gout attacks.[1]
- There is moderate evidence that long-term ULT should not be initiated in the majority of patients after the initial attack or in patients with infrequent attacks.[4]
- Evidence is insufficient to make conclusions on efficacy or safety in specific subgroup populations.[1]

- In 11 trials evaluating the safety of allopurinol and ULT combination therapy, most adverse reactions were of mild to moderate severity.[2] Moderate evidence found elevated liver function tests were the most common adverse event leading to withdrawal in studies of allopurinol and febuxostat. There is moderate evidence that more probenecid-treated patients compared to allopurinol discontinued therapy (26% vs. 11%). Allopurinol was associated with a 7% incidence of withdrawal due to rash compared to 3% with probenecid; however, gastrointestinal (GI) adverse reactions were more common with probenecid compared to allopurinol (23% vs. 7%, respectively).[2]
- Harms associated with acute gout treatment were GI adverse reactions experienced with colchicine and NSAIDs and both need dose reductions in patients with renal impairment. Systemic corticosteroids and adrenocorticotropic hormone (ACTH) derivatives were associated with elevated blood glucose levels, dysphoria, immune suppression, and fluid retention with short-term use.[1] Adverse events were found to be similar between allopurinol (300 mg) and febuxostat 40 mg based on high level evidence. Most common adverse events were rash (sometimes serious) and abdominal pain with allopurinol and diarrhea and musculoskeletal pain with febuxostat (and rarely skin reactions).

Recommendations:

- Continue preferred drug list (PDL) status for allopurinol as the first-line ULT.
- Recommend clinical prior authorization (PA) criteria for non-preferred drugs (**Appendix 3**).
- No other changes to the OHP PDL are recommended based on current evidence. Review comparative drug costs in the executive session.

Previous Conclusions:

- There is low quality evidence a greater proportion of patients respond to treatment, defined as a 50% or greater decrease in pain score, with high-dose (4.8 mg over six hours) colchicine compared to placebo (absolute risk difference 28%; RR 2.16; 95% CI 1.28 to 3.65; NNT 4) and low quality evidence significantly decreases inflammation scores more than placebo (absolute risk difference 45%; RR 10.50; 95% CI 1.48 to 74.38).
- There is low quality evidence of no significant difference between high- (4.8 mg over six hours) and low-dose (1.8 mg over one hour) colchicine in treatment response (RR 0.86; 95% CI 0.53 to 1.41) with fewer gastrointestinal events with low-dose colchicine.[1]
- There is insufficient evidence of any significant difference between allopurinol and febuxostat for treatment of acute gout flares.
- There is low-quality evidence of uncertainty around the difference in prevention of acute gout attacks between probenecid and allopurinol after 18 months of treatment (53% vs. 55%; RR 0.96; 95% CI 0.53 to 1.75) with no significant difference found.

- The U.S. Food and Drug Administration (FDA) approved lesinurad 200 mg daily as an adjunct with a xanthine oxidase inhibitor (allopurinol or febuxostat) for hyperuricemia based on 3 unpublished, multinational, phase 3 clinical trials of unclear risk of bias and uncertain applicability. Though the 400 mg daily dose was studied, the FDA denied approval of the dose based on increased risk for major cardiovascular and renal events compared to placebo.
    - There is insufficient comparative evidence that lesinurad is superior to existing anti-gout agents when used in combination with a xanthine oxidase inhibitor.
    - There is insufficient evidence that lesinurad in combination with a xanthine oxidase inhibitor demonstrates efficacy in reduction of gout flares, provides symptom relief, results in function improvement, or improves health-related quality of life versus a xanthine oxidase inhibitor alone.
    - There is insufficient evidence for use of lesinurad as monotherapy for management of hyperuricemia.
    - There is low quality evidence that daily doses of lesinurad 200 mg in combination with allopurinol may result in over half of patients achieving a serum uric acid less than 6 mg/dL over 6 months [54% vs. 28% with placebo, respectively; RR 0.26 (95% CI, 0.17 to 0.36; p<0.0001) and 55% vs. 23%, respectively; RR 0.32 (95% CI, 0.23 to 0.41; p<0.0001)]; similarly, in combination with febuxostat, there is low quality evidence adjunctive use of lesinurad 200 mg daily may result in over half of patient achieving a serum uric acid less than 5 mg/dL over 6 months [57% vs. 47% with placebo; RR 0.10 (95% CI, -0.03 to 0.23; p=0.1298)]. Lesinurad did show statistically significant reductions in serum uric acid levels relative to placebo over 6 months (range -0.79 to -1.08 mg/dL). The clinical significance of these reductions and how it relates to prevention of gouty attacks is unclear.
    - There is moderate quality evidence that lesinurad treatment is associated with an increased risk of renal adverse events, including reversible and non-reversible elevations in serum creatinine and acute renal failure.
    - There is insufficient evidence that any subgroups based on a particular demographic may benefit from lesinurad more than the general population for which it has been studied. All patients studied were adults, mostly obese white males between 21 to 82 years of age.

Previous Recommendations:

- Continue to include one xanthine oxidase inhibitor as preferred on the PDL for the treatment of chronic gout and hyperuricemia.
- Maintain Zurampic® (lesinurad) as non-preferred on the PMPDP.

Background:

Gout is the most common form of inflammatory arthritis.[5] The pathophysiology of gout stems from rising serum urate levels that exceed the saturation point in the blood leading to crystals that deposit in cartilage, bones, tendons and other sites. This increase in serum urate can be from overproduction or reduced excretion of uric acid resulting in inflammatory joint swelling and pain.[1] The American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classifies gout based on presence of monosodium urate monohydrate (MSU) crystals in the symptomatic joint, bursa or tophi or at least 1 episode of swelling, pain or tenderness in a peripheral joint or bursa with additional clinical criteria also being met.[6] The ACP recommends synovial fluid analysis in patients with acute gout when diagnostic testing is indicated.[7]

Gout is characterized by acute attacks (lasting 7-14 days) that are self-limiting and are accompanied by symptoms of pain and inflammation that often presents in the toe but can occur in other joints. Chronic gout stems from acute attacks that increase in duration and become persistent.[1] Asymptomatic hyperuricemia can also occur; however, there is no evidence to support treatment as a preventative strategy for progression to symptomatic gout.[1] The risk of acute gout attacks can be predicted by serum urate levels. Guidelines recommend serum urate levels less of than 6 mg/dL for patients with gout and less than 5 mg/dL in patients with significant gout.[1,3,8] Tophi, which are uric acid crystals that deposit in the joints and other areas, may develop in patients with chronic gout and hyperuricemia. Important outcomes to consider when assessing treatment for gout are: serum and/or uric acid levels, gout attacks, development of tophi, and progression from acute to chronic gout.

Risk factors for the development of gout include obesity, excessive alcohol intake, dietary factors, medications that increase uric acid levels and chronic kidney disease.[4] Patients with a diagnosis of gout are advised to avoid organ meats, high fructose corn syrup-sweetened sodas and other foods, alcohol overuse, and alcohol abstinence during acute gout attacks.[8] Patients are also encouraged to minimize impact of comorbidities by optimizing weight, regular exercise, diet modifications, minimal alcohol consumption, and treatment of underlying cardiovascular (CV) risk factors.[9]

Selection of gout therapies is dependent on the diagnosis of acute or chronic gout (Table 1).[1,3,9] Treatment for acute gout should be initiated within 24 hours of the onset of the attack.[5] The ACR recommends treatment based on severity of pain and the number of joints involved.[5] Monotherapy with oral NSAIDS, systemic corticosteroids, or colchicine is recommended for mild to moderate severity of acute gout (visual analog score [VAS] of less than 6 and involvement in 1-3 small joints or 1-2 large joints). Combination therapy is indicated for polyarticular attacks with severe pain. Combination options in severe cases include: 1) NSAIDs and colchicine; 2) oral corticosteroids and colchicine; or 3) intra-articular steroids and one of the other oral treatment options.[1,5] In severe refractory cases of gout, use of a biologic interleukin-1 (IL-1) inhibitor can be considered. ACTH subcutaneous injections can be an option in patients who are not able to take medications by mouth.[5]

Management of chronic gout focuses on urate reduction through ULT (table 1).[1,3,9] Guidelines recommend ULT in patients with a gout diagnosis and the following: tophus or tophi, frequent attacks (≥ 2 attacks/year), chronic kidney disease stage 2 or worse or a history of past urolithiasis.[8] Serum urate levels should be checked every 2-5 weeks during the titration phase and every 6 months once a maintenance dose is determined. Xanthine oxidase inhibitors (XOI), allopurinol and febuxostat, are recommended as first-line pharmacological treatment options. Alternative pharmacological options are uricosurics (probenecid and lesinurad).[5] Guidelines prefer an XOI over uricosurics for chronic gout. Lesinurad is an alternative to probenecid due to limited evidence of efficacy and renal concerns, such as reversible and non-reversible elevations in serum creatinine and acute renal failure. Combination therapy with a XOI and probenecid are recommended if XOI monotherapy fails to lower serum urate levels to target.[8] If patients develop an acute gout attack on ULT, recommendations are to continue ULT while treating the acute attack.

Combination therapy with ULT and acute gout medications are recommended for patients experiencing symptoms of an acute attack and are candidates for chronic treatment. Historically, it is recommended that ULT be started 2 weeks after an acute flare subsides, as ULT may increase acute gout attacks initially; however, there is limited evidence that this delay is not required.[8] Low dose colchicine is recommended first-line for prophylaxis and low dose NSAIDs as a first-line alternative. Low dose prednisone or prednisolone are also used as an alternative to first-line agents in some patients.[5] Prophylaxis is recommended for at least 6 months. Dietary factors (alcohol use, meat intake, shellfish intake, intake of high fructose foods) have shown to play a role in the risk for gout and can be recommended as adjunctive measures to pharmacotherapy.

Table 1. Treatments used for the Management of Gout[1,8,5,10]

Drug	Mechanism of Action
Acute Gout Management	
NSAIDs†	Anti-inflammatory
Corticosteroids (intraarticular or oral†)	Anti-inflammatory
Colchicine†	Microtubule disrupting agent
Pituitary adrenocorticotropic hormone (ACTH)	Anti-inflammatory

Urate-lowering therapy (ULT)	
Allopurinol	Xanthine oxidase inhibitor
Febuxostat	Xanthine oxidase inhibitor
Probenecid	Uricosuric - prevention of renal reabsorption of uric acid and increase excretion
Lesinurad*	Uricosuric – increase excretion of uric acid
* To be used as an adjunct with a xanthine oxidase inhibitor † Also recommended for gout prophylaxis	

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), Cochrane Collection, 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:

AHRQ – Management of Gout
In March of 2016, AHRQ completed a systematic review on the management of gout in adult patients with a focus on the primary care setting. Included studies were assessed for risk of bias using the Cochrane Risk of Bias Tool and a modified AMSTAR tool was used for the determination of the quality of systematic reviews.[1] Key questions focused on the treatment of acute gout, dietary and lifestyle management of gout, pharmacological management of hyperuricemia in gout patients, treatment and monitoring of patients with gout and discontinuation of treatment for patients on acute or chronic gout medications. Results of the literature search yielded 143 articles for inclusion into the review.[1] The study population included in the analysis was deemed to have moderate applicability to patients seen in primary care. Eight percent of the included studies specifically stated that patients were from the primary care setting which have been shown to have at least 10% less incidence of tophi compared to trials including patients from other settings such as hospitals.

Acute Gout Treatment
For the treatment of acute gout, 15 studies were included, 10 were systematic reviews and 5 were randomized controlled trials. The randomized controlled trials were small with the number of participants ranging from 57-190. Study participants were adult patients with a diagnosis of acute gout. About 90% of participants were male with a mean age of 54 years (when reported). Findings related to specific drug therapies are presented in Table 1.[1] There was insufficient evidence for the outcomes of joint swelling, tenderness, activities of daily living, and patient global assessment. Assessment of efficacy based on patient demographics, comorbid conditions, disease severity, clinical presentation or lab values was insufficient. Colchicine and NSAIDs were associated with GI adverse

events and require dose reductions in patients with renal impairment. Systemic corticosteroids and ACTH derivatives were associated with elevated blood glucose levels, dysphoria, immune suppression, fluid retention.[1]

Table 2. Evidence for Drugs Used in Acute Treatment of Gout[1]

Drugs *(i.e., NSAIDs, corticosteroids, colchicine, ACTH, IL-1B receptor antagonists*)*	**Findings**	**Strength of evidence**
Colchicine	Pain relief	High
Low-dose colchicine (1.2 mg initially followed by 0.6 mg one hour later) vs. high-dose colchicine (1.2 mg initially followed by 0.6 mg each hour for the next 6 hours)	Pain relief similar with less adverse events in low-dose group	Moderate
NSAIDs	Pain relief	High
NSAIDs	Similar effectiveness between all NSAIDs used for gout	Moderate
Systemic corticosteroids	Pain relief	High
Animal-derived ACTH formulations *(i.e., corticotropin [H.P. Acthar® Gel])*	Pain relief	Moderate
** No new evidence was found for IL-1B receptor antagonists*		

Dietary and Lifestyle Management of Gout

Six new trials, 3 observational studies and 5 systematic reviews evaluated the role of diet in gout, including Traditional Chinese Medicine (herbs and acupuncture).[1] Randomized controlled trials ranged from 29-1042 participants, with the larger studies funded by Beijing University of Chinese Medicine. Evidence on the impact of dietary changes on improving gout symptoms was insufficient. Similarly, evidence for the reduction of serum urate levels as a result of dietary changes was insufficient. The role of Traditional Chinese Medicine provided insufficient evidence in treating the symptoms of gout.

Hyperuricemia Management in Patients with Gout

Forty-five studies provided evidence on efficacy and safety of pharmacological hyperuricemia management.[1] Evidence for ULT were based on studies with low to high risk of bias in adult patients with chronic gout. Findings for efficacy outcomes are the following:

- There is high strength of evidence of no difference in serum urate lowering between febuxostat 40 mg and allopurinol 300 mg.
- There is high strength of evidence that prophylaxis with low dose colchicine or low dose NSAIDs at the start of ULT initiation, reduces the risk of an acute gout attack by a similar amount.
- There was insufficient evidence to determine the effect of feboxostat compared to allopurinol 300 mg on the presence of tophi.
- Moderate strength of evidence supports longer treatment courses (>8 weeks) of colchicine or NSAIDs, with ULT, for gout attack prevention compared to shorter courses.

High strength evidence shows that the risk of acute gout attacks is not reduced with ULT within the first 6 months; however, attacks were decreased after approximately 1 year of ULT based on moderate evidence. The use of ULT does indeed decrease serum urate levels based on high strength evidence.[1] The evidence for the role of dietary changes on serum urate levels are insufficient. Adverse events most associated with ULT are rash for allopurinol (sometimes

serious) and abdominal pain, diarrhea and musculoskeletal pain (and rarely skin reactions) with febuxostat. Risk of adverse events were found to be similar between allopurinol (300 mg) and febuxostat 40 mg based on high strength evidence.

Monitoring Treatment for Gout

Twenty-six studies provided evidence for monitoring treatment in patients with gout.[1] The evidence was insufficient to correlate serum urate levels with outcomes. There was low level evidence that targeting a specific urate level reduces the risk of gout attacks.

Discontinuing Treatment for Acute and Chronic Gout

Only three studies were identified that discussed discontinuing gout treatment.[1] Moderate evidence supports the use of at least 8 weeks of NSAIDs or low dose colchicine prophylaxis for acute gout when starting ULT to reduce the risk of gout attacks. The evidence related to the most appropriate time to discontinue treatment is insufficient to draw firm conclusions.

Safety of Allopurinol Versus Other ULT

A systematic review and meta-analysis analyzed the safety of using allopurinol with ULT in patients with gout.[2] Patients included were at least 18 years of age and had a gout diagnosis as defined by the ACR (a) the presence of characteristic urate crystals in the joint fluid and/or b) a tophus proved to contain urate crystals by chemical or polarized light microscopic means, and/or c) the presence of clinical, laboratory, and X-ray phenomena outline by ACR) or evidence of urate crystals in the synovial fluid.[11] The primary outcomes studied were rates of adverse events and death. Seven randomized trials met inclusion criteria and were graded according to the Jadad scale and 4 systematic reviews were also included. Five studies were considered moderate in quality and 2 were high quality. Over 80% were males with a mean age 69 years. Comparisons to allopurinol (max dose 300 mg/day) included placebo, febuxostat (40-240 mg), probenecid and benzbromarone (not available in the US).[2] Abnormal liver function, diarrhea and rash were the most commonly reported adverse events. Overall most adverse events were mild to moderate in severity. In comparisons of allopurinol to febuxostat, the adverse events were similar between groups. Withdrawal rates were similar between groups with the most common reason being abnormal liver function tests (LFTs); however, high-dose febuxostat (120 mg) was associated with significantly higher withdrawal rates due to increased LFTs.[2] Cardiovascular events were rare: one event each were found with allopurinol, placebo and febuxostat 240 mg groups and 5 events in the febuxostat 80 mg and 120 mg groups. In a comparison of allopurinol to probenecid, higher rates of discontinuation were found in probenecid-treated patients compared to allopurinol (26% vs. 11%). Allopurinol was associated with a higher incidence rate and withdrawal due to rash compared to probenecid (7% vs. 3%); however, GI adverse reactions were more common with probenecid compared to allopurinol (23% vs. 7%). There was heterogeneity amongst the included studies, making comparisons of results difficult. Additionally, lower doses of allopurinol were used in most studies.[2]

New Guidelines:

EULAR 2016 Guideline on the Management of Gout

Updated EULAR guidelines on the management of gout were published this year.[3] Fifty-one references were analyzed and 11 recommendations were produced (Table 4). Evidence to support recommendations were based on *categories of evidence* and *strength of the recommendation*. The categories were graded from 1A to 4, with 1A being the highest level of evidence (meta-analysis of randomized trials) and 4 being expert opinion (Table 3). The category of evidence was used to develop the strength of the recommendations as outlined in Table 4. [3]

Table 3. EULAR Categories of Evidence

Category	Evidence
1A	From meta-analysis from randomized controlled trials
1B	From at least one randomized controlled trial
2A	From at least one controlled study without randomization
2B	From at least one type of quasi-experimental study
3	From descriptive studies, such as comparative studies, correlation studies or case-control studies
4	From expert committee reports or opinions and/or clinical experience of respected authorities

Table 4. EUAR Strength of Recommendation

Strength	Directly based on
A	Category I evidence
B	Category II evidence or extrapolated recommendations from category I evidence
C	Category III evidence or extrapolated recommendations from category I or II evidence
D	Category IV evidence or extrapolated recommendations from category II or III evidence

General overarching principles were that every patient should receive education on pathophysiology, treatments for gout, importance of SUA levels and comorbidities associated with gout. Additionally, the role of weight loss and diet (avoidance of alcohol, meat and seafood intake and sugar-sweetened drinks) and importance of exercise should be discussed.[3] It is advised that all patients with gout are screened for comorbidities and cardiovascular risk factors, such as: renal impairment, coronary heart disease, heart failure, stroke, peripheral arterial disease, obesity, hyperlipidemia, hypertension, diabetes and smoking. The recommendations and strength of the treatment recommendations are presented below (Table 5). Treatment algorithms for the management of acute gout and hyperuricemia are presented in Figures 1 and 2.

Table 5. 2016 EULAR Recommendations for the Treatment of Gout.[3]

Recommendation	Strength of Recommendation
1. Acute gout flares should be treated as soon as possible. Colchicine should be given as soon as possible, within 12 hours of symptom onset	D A
2. First-line options for acute gout flares: - Colchicine (except with severe renal impairment) and/or - NSAID (except with severe renal impairment); or - Oral corticosteroid; or - Articular aspiration and injection of corticosteroids	 A A A C
3. Frequent flares with contraindications to medications in #2 should be considered for IL-1 blockers - Recommendation based on evidence for canakinumab (not available in the US)	 A

- Evidence from anakinra	C
4. Acute gout prophylaxis is recommended in the first 6 months of ULT with colchicine (0.5-1 mg/day in patients with normal renal function). Use low dose NSAIDs as an alternative if not contraindicated.	B
5. ULT is indicated for patients with recurrent flares, tophi, urate arthropathy and/or renal stones. Patients at high risk should be offered ULT at time of diagnosis.	A
6. Patients taking ULT should have SUA levels maintained to < 6 mg/dL. Patients with severe gout should have target SUA levels of < 5 mg/dL (levels < 3 mg/dL long-term are not recommended).	C
7. ULT should be started at a low dose and titrated to SUA levels of < 6 mg/dL which should be maintained for life.	C
8. First-line option for ULT is allopurinol 100 mg/day (in patients with normal renal function), increasing dose by 100 mg every 2-4 weeks if needed. - If SUA target is not obtained with allopurinol then the patient should be switched to febuxostat **OR** - an uricosuric (probenecid or lesinurad) may be used alone or added to allopurinol.	A A B
9. Allopurinol doses should be adjusted in patients with renal impairment according to creatinine clearance.	C
10. Pegloticase injection is only indicated for patients who have not been able to obtain target SUA levels on other treatments, alone or in combination at maximal doses, and also have crystal-proven, severe debilitating chronic tophaceous gout and poor quality of life.	A
11. In patients on loop or thiazide diuretics who develop gout, alternative agents should be considered if possible.	C

Figure 1. Management of Gout Flares

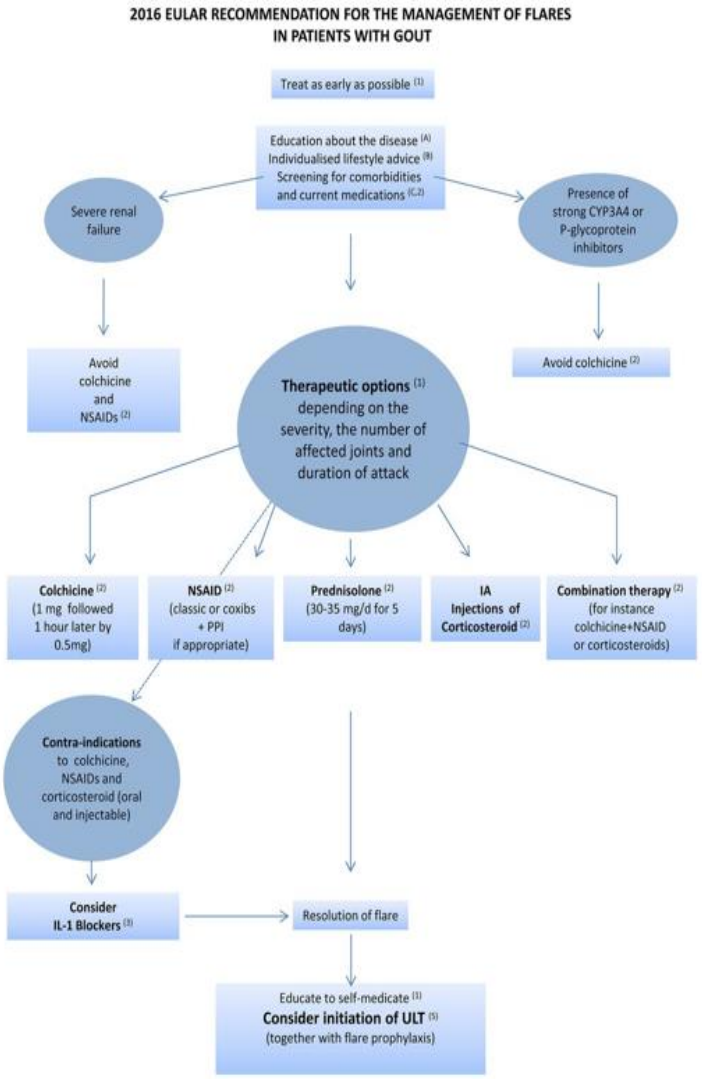
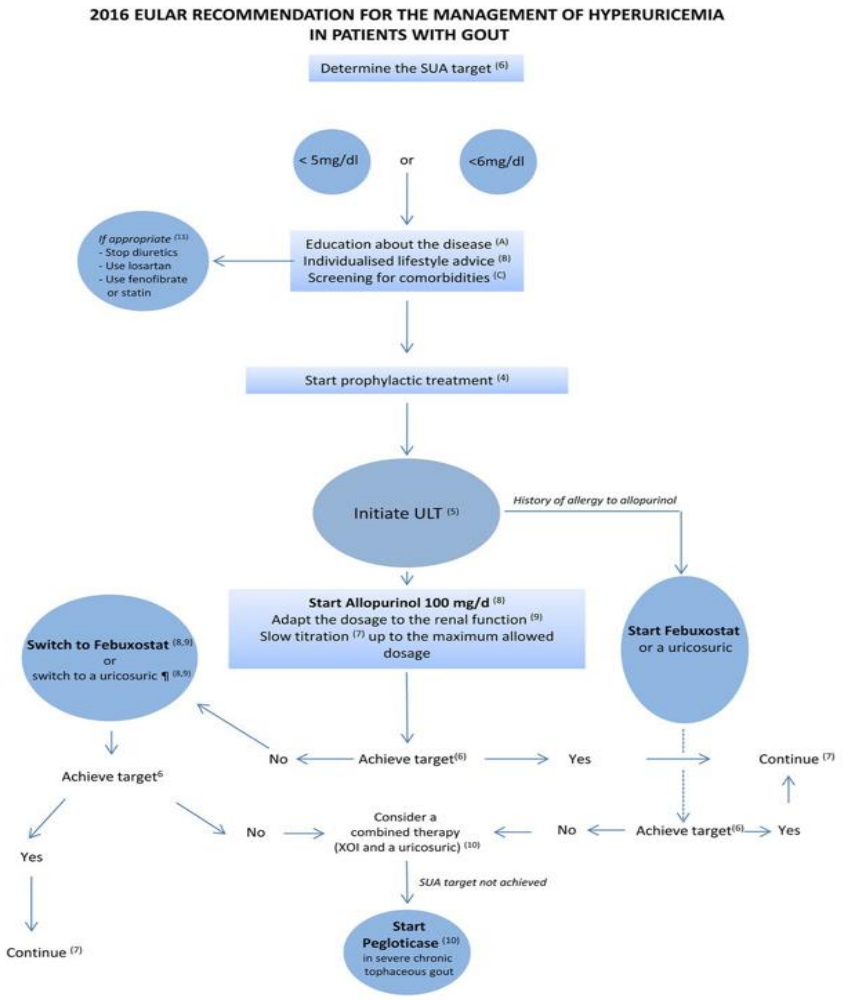


Figure 2. Management of Hyperuricemia



Richette P, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. Ann Rheum Dis 2016. DOI: 10.1136/annrheumdis-2016-209707

American College of Physicians Management of Gout Guidelines

Guidelines for the management of acute and recurrent gout were published by the ACP.[4] The evidence was reviewed and evaluated according to ACP grading system. Recommendations were based on the AHRQ guidance presented above. Four recommendations were outlined by ACP.

1) Corticosteroids, NSAIDs or colchicine should be used for pain treatment in acute gout based on high strength of evidence.
    a. Corticosteroids are recommended as first-line because of safety and cost. NSAIDs are also very effective for pain associated with gout and moderate evidence found no difference between NSAIDs. Indomethacin is often thought as the first-line NSAID for gout but there is no evidence that it provides superior efficacy. Colchicine is an option but is more expensive than comparative treatments.
2) Low-dose colchicine is recommended when using colchicine for acute gout treatment based on moderate evidence.
    a. Colchicine 1.2 mg followed by 0.6 mg 1 hour later has been shown to be as effective for pain management as colchicine 1.2 mg followed by 0.6 mg/hour for 6 hours. Low-dose colchicine has also been shown to have a lower risk of GI adverse events compared to high-dose regimens.
3) Long-term ULT is not recommended for most patients after the first gout attack or for those with infrequent attacks based on moderate evidence.
    a. There is insufficient evidence to support the use of ULT long-term (>12 months) in patients with single or infrequent gout attacks.
4) Benefits, harms, costs and individual preferences should be discussed with patients before initiating ULT, including concomitant prophylaxis, based on moderate evidence.
    a. If ULT is appropriate, febuxostat (40 mg) and allopurinol (300 mg) offer similar serum urate lowering.
    b. There is insufficient evidence on the optimal duration of ULT; however, evidence supports a reduction in acute gout attacks after 1 year but not within the first 6 months.
    c. At least 8 weeks of prophylactic therapy with low-dose colchicine or NSAIDs has been shown to reduce the incidence of acute gout attacks in patients starting ULT.

New Safety Alerts:
No new safety alerts identified.

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

Randomized Controlled Trials:
A total of 85 citations were manually reviewed from the literature search. After manual review, all trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical).

References:

1. Shekelle P, FitzGerald J, Newberry S. Managment of Gout. *Comparative Effectiveness Review No 176 AHRQ Publication*. 2016;No. 16-EHC017-EF.

2. Castrejon I, Toledano E, Rosario MP, Loza E, Perez-Ruiz F, Carmona L. Safety of allopurinol compared with other urate-lowering drugs in patients with gout: a systematic review and meta-analysis. [Review][Erratum appears in Rheumatol Int. 2015 Jul;35(7):1139; PMID: 25895647]. *Rheumatology International*. 2015;35(7):1127-1137. doi:10.1007/s00296-014-3189-6.

3. Richette P, Doherty M, Pascual E, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. *Ann Rheum Dis*. July 2016:annrheumdis-2016-209707. doi:10.1136/annrheumdis-2016-209707.

4. Qaseem A, Harris RP, Forciea MA, Clinical Guidelines Committee of the American College of Physicians. Management of Acute and Recurrent Gout: A Clinical Practice Guideline From the American College of Physicians. *Ann Intern Med*. November 2016. doi:10.7326/M16-0570.

5. Khanna D, Khanna PP, Fitzgerald JD, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and antiinflammatory prophylaxis of acute gouty arthritis. *Arthritis Care Res (Hoboken)*. 2012;64(10):1447-1461. doi:10.1002/acr.21773.

6. Neogi T, Jansen TLTA, Dalbeth N, et al. 2015 Gout classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis*. 2015;74(10):1789-1798. doi:10.1136/annrheumdis-2015-208237.

7. Qaseem A, McLean RM, Starkey M, Forciea MA, Clinical Guidelines Committee of the American College of Physicians. Diagnosis of Acute Gout: A Clinical Practice Guideline From the American College of Physicians. *Ann Intern Med*. November 2016. doi:10.7326/M16-0569.

8. Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res (Hoboken)*. 2012;64(10):1431-1446. doi:10.1002/acr.21772.

9. Jordan KM, Cameron JS, Snaith M, et al. British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of gout. *Rheumatology (Oxford)*. 2007;46(8):1372-1374. doi:10.1093/rheumatology/kem056a.

10. Zurampic (lesinurad) [Prescribing Information]. Wilmington, DE: AstraZeneca.

11. Wallace SL, Robinson H, Masi AT, Decker JL, McCarty DJ, Yü TF. Preliminary criteria for the classification of the acute arthritis of primary gout. *Arthritis Rheum*. 1977;20(3):895-900.

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	TABLET	ALLOPURINOL	ALLOPURINOL	Y
ORAL	TABLET	ZYLOPRIM	ALLOPURINOL	Y
ORAL	TABLET	PROBENECID-COLCHICINE	COLCHICINE/PROBENECID	Y
ORAL	CAPSULE	COLCHICINE	COLCHICINE	N
ORAL	CAPSULE	MITIGARE	COLCHICINE	N
ORAL	TABLET	COLCHICINE	COLCHICINE	N
ORAL	TABLET	COLCRYS	COLCHICINE	N
ORAL	TABLET	ULORIC	FEBUXOSTAT	N
ORAL	TABLET	ZURAMPIC	LESINURAD	N
ORAL	TABLET	PROBENECID	PROBENECID	N

Appendix 2: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) without Revisions** 1996 to September Week 3 2016

Search Strategy:

#	Searches	Results	Annotations
1	Allopurinol/	3272	
2	Colchicine/	4195	
3	Probenecid/	697	
4	Febuxostat/	258	
5	lesinurad.mp.	10	
6	1 or 2 or 3 or 4 or 5	8168	
7	limit 6 to (english language and humans and yr="2015 -Current")	323	
8	limit 7 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial or comparative study or controlled clinical trial or meta analysis or practice guideline or randomized controlled trial or systematic reviews)	85	

Agents for Gout

Goal(s):

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

Length of Authorization:

Up to 12 months

Requires PA:

- Non-preferred drugs

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Will the provider switch to a preferred product? Preferred products for the treatment of acute gout flares, gout prophylaxis and chronic gout are available without a PA. Note: Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in the class	**No:** Go to #3
3. Is the treatment request for an acute flare of gout?	**Yes:** Go to #4	**No:** Go to #6
4. Has the patient tried and failed NSAID therapy or have contraindications to NSAIDs?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; recommend trial of NSAID

Approval Criteria		
5. Is the request for colchicine?	**Yes:** Approve for 12 months	**No:** Go to #6
6. Is the treatment request for colchicine for prophylaxis of gout?	**Yes:** Go to #7	**No:** Go to #8
7. Has the patient tried and failed NSAID therapy or have contraindications to NSAIDs?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; recommend trial of NSAIDs
8. Is the request for febuxostat and the patient has tried and failed allopurinol or has contraindications to allopurinol?	**Yes:** Approve for 12 months	**No:** Go to #9
9. Is the request for lesinurad and the patient has tried and failed allopurinol AND febuxostat or has contraindications to both treatments?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; recommend trial of allopurinol and/or febuxostat

P&T Review: *1/17 (KS)*
Implementation: *TBD*

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Class Review: Conventional Antiemetics

Date of Review: January 2017

Purpose for Class Review:
The purpose of this class review is to evaluate the evidence for the safety and efficacy of conventional antiemetics in reducing nausea and vomiting (n/v) associated with gastroenteritis, motion sickness, migraine headache, pregnancy, surgery, and chemotherapy. This review will also help determine the role of these agents compared to newer antiemetics. In addition, an evaluation of use of conventional antiemetics for unfunded conditions will be completed.

Research Questions:
1. What is the comparative efficacy and effectiveness of conventional antiemetic treatments (dimenhydrinate, dronabinol, meclizine, metoclopramide, nabilone, prochlorperazine, promethazine, scopolamine and trimethobenzamide) in reducing n/v associated with pregnancy, chemotherapy, surgeries, gastroenteritis, migraine headaches or motion sickness?
2. What are the comparative harms of conventional antiemetic treatments used in patients with n/v?
3. Are there subpopulations of patients in which a particular antiemetic treatment would be more effective or associated with less harm?
4. What diagnoses in Oregon Health Plan (OHP) patients are most commonly associated with conventional antiemetic claims?

Conclusions:
- For adults experiencing n/v due to gastroenteritis, there is insufficient evidence to support the superiority of any one antiemetic over another, or the superiority of any drug over placebo.
- There is moderate quality evidence that scopolamine is effective in preventing motion sickness compared to placebo. No conclusions or recommendations can be made on the comparative effectiveness of scopolamine and other agents such as meclizine or dimenhydrinate.
- Pyridoxine is recommended as first-line therapy for pregnant women with nausea. Retrospective studies have evaluated the risks to the fetus of the use ondansetron in pregnant women and it appears to be safe for use in pregnancy based on this low quality evidence.
- There is moderate quality evidence that 5HT-3 receptor antagonists are superior to conventional antiemetics in managing post-operative nausea and vomiting (PONV). Moderate quality evidence also shows that transdermal scopolamine is effective in reducing PONV.
- There is moderate quality evidence that metoclopramide is an effective adjunct in combination with aspirin in managing nausea associated with migraine headaches.
- Management of chemotherapy induced nausea and vomiting (CINV) should include an assessment of the emetogenicity of the chemotherapy. High quality evidence demonstrates 5-HT3 receptor antagonists and neurokinin-1 receptor antagonists are effective at reducing CINV.
- Low quality evidence demonstrates that cannabinoids may be effective in controlling refractory CINV, however their use may be limited by adverse effects.

- Approximately 12% of the conventional antiemetic utilization in the state of Oregon's fee-for-service (FFS) Medicaid population is for unfunded conditions including vertigo, motion sickness, GERD, and noninfectious gastroenteritis.

Recommendations:

- Add conventional antiemetics to the Oregon Health Plan (OHP) fee-for-service practitioner-managed prescription plan.
- Designate scopolamine, dimenhydrinate, and meclizine as non-preferred since these drugs are primarily prescribed for nonfunded conditions.
- PDL status for other conventional antiemetics may be informed after comparative drug costs of conventional antiemetics in the executive session.
- Nonpreferred antiemetics and select preferred antiemetics that exceed specific quantity limits are already subject to the current clinical prior authorization (PA) criteria in **Appendix 5**. Consolidation of clinical PA criteria for newer antiemetics and dronabinol into one policy requires approval by the Committee (see **Appendix 4**). Non-preferred conventional antiemetics will also be subject to this policy.

Background:

A class update of newer antiemetics was presented at the January 2016 Pharmacy and Therapeutics Committee meeting and primarily focused on comparative efficacy and effectiveness of 5-hydroxytryptamine-3 (5-HT3) and P/neurokinin 1 (NK1) receptor antagonists. Conventional antiemetics including dimenhydrinate, trimethobenzamide, scopolamine, meclizine, metoclopramide, prochlorperazine and promethazine have not previously been reviewed by the P&T Committee yet there is significant use of these agents in the fee-for-service population. The cannabinoids nabilone and dronabinol will also be reviewed with the conventional antiemetics.

Vomiting associated with pregnancy (line 1), complications associated with migraine headaches (line 415) or enteric infections and other bacterial food poisoning (line 150) are funded diagnoses on the OHP List of Prioritized Services.[1] Vertigo (line 515), gastroparesis (line 531) and noninfectious gastroenteritis (line 555) are not funded by OHP. A complete list of list of antiemetic indications and their associated OHP funding line is included in table 5 of **Appendix 3**.

A retrospective report of conventional antiemetic claims was generated to assess use of these agents over 1 year from October 2014 through September 2015. During this time frame, there were 7,364 claims for 4,330 separate patients which were associated with a total cost of $134,500 to the OHP. Dronabinol is the only medication from this class that requires prior authorization (PA). Dronabinol comprised approximately 1% of the conventional antiemetic use but was associated with 32% of total claim costs during this time frame. Sixty-two percent of all antiemetic claims were for promethazine. The second most utilized agent was metoclopramide with 13% of total claims. A review of the antiemetic indications reveals that more patients received therapy for funded (30.4%) conditions than unfunded (11.8%) conditions. Most of the claims for funded indications were for PONV (24.8%). For unfunded diagnoses, vertigo (5.7%) was the primary associated diagnosis with antiemetic therapy. One of the limitations of this report is that diagnoses information is separate from prescription claims. Over half of the patients (57.8%) did not have a diagnosis associated with the antiemetic claims. The complete report can be reviewed in tables 6 and 7 of **Appendix 3**.

Promethazine abuse has been reported in several sources.[2,3] Promethazine may be misused by itself or in conjunction with opioids. In an 11 year retrospective review by the Maryland Poison Center 354 single product abuse or misuse exposures of promethazine were documented in the National Poison Data System.[3] A report was compiled from Oregon Medicaid Fee claims processed January 2016 through June 2016 to evaluate the possible correlation between antiemetic use and substance abuse. Fifty five percent of the patients receiving an antiemetic also had a claim for an opioid. Seventeen percent of this population also had a recent history (within the past 18 months) of substance abuse. Nine percent of the patients identified in this cohort had at least one antiemetic, but no opioids in the past six months and a history of substance abuse. This data reveals a possible connection between antiemetic utilization and substance abuse, however more evidence should be compiled to provide an accurate assessment of this potential issue. The details of the report can be reviewed in table 8 of **Appendix 3.**

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. Conventional Antiemetic Indications and Dosing.[4,5]

Drug Name (Trade Name)	Indication(s)	Rx/OTC	Strength/Route	Dose and Frequency (Adults)
Dimenhydrinate (Dramamine, Driminate, Motion Sickness)	Motion sickness N/V Vertigo	OTC (tablets) Rx (injection)	50 mg tablet 50 mg chewable tablet 50 mg/mL IV solution	50-100 mg po q4-6h 50-100 mg IM/IV q4-6h Maximum 400 mg/day
Dronabinol (Marinol)	AIDS ; loss of appetite CINV	Rx – Schedule III	2.5 mg, 5 mg, 10 mg capsule	2.5 mg po BID 5 mg/m^2 po q2-4 prn Maximum 20 mg per day
Meclizine (Antivert, Motion Relief)	Motion sickness RINV Vertigo	OTC	12.5 mg and 25 mg tablet 25 mg chewable tablet	25-50 mg po x1 prn 50 mg po 2-12 hour prior to imaging 25-100 mg per day in divided doses
Metoclopramide (Reglan)	CINV PONV GERD Diabetic gastroparesis	Rx	5 mg and 10mg tablet 5 mg and 10 mg rapid dissolve tablet 5 mg/mL IV solution 1 mg/mL oral solution	1-2 mg/kg/dose IV prn 10-20 mg IV q4-6h 10-15 mg po q6h (max 12 weeks) 10 mg po q6h (max 12 weeks)
Nabilone (Cesamet)	CINV	Rx –Schedule II	1 mg capsule	1-2 mg po BID Maximum 6 mg per day
Phosphoric Acid/Dextrose/Fructose (Formula EM, Emetrol)	Nausea	OTC	120 mL oral solution (fructose 1.87 gm, dextrose 1.87 gm, and phosphoric acid 21.5 mg/5 mL)	15-30 mL po q15 min Maximum 5 doses/hour
Prochlorperazine (Compazine)	Severe N/V	Rx	5 mg and 10 mg tablet 5 mg/mL vial 25 mg suppository	5-10mg po TID-QID 2.5 mg – 10mg IV q6h prn 5-10mg IM q6h prn 25 mg PR BID Maximum 40 mg per day
Promethazine (Phenergan)	Nausea/Vomiting Motion Sickness Vertigo	Rx	25 mg/mL and 50 mg/mL vial 6.25 mg/5 mL oral solution 12.5 mg, 25 mg, 50 mg tablet 12.5 mg, 25 mg, 50 mg suppository	*Dose varies by indication* 12.5 – 25 mg IM/IV q4-6h prn 12.5-25 mg po q4-6h prn 12.5-25 mg PR q4-6h prn 25 mg po BID 25 mg PR BID
Scopolamine (Transderm-Scop)	Motion Sickness PONV	Rx	1.5 mg extended release patch	1 patch every 3 days
Trimethobenzamide (Tigan)	Gastroenteritis PONV	Rx	250 mg and 300 mg capsule 100 mg/mL vial	300 mg po TID-QID 200 mg IM TID-QID

Abbreviations: BID = twice daily; CINV = chemotherapy-induced nausea and vomiting; IM = intramuscularly; IV = intravenously; n/v = nausea and vomiting; OTC = over-the-counter; PONV = post-operative nausea and vomiting; PO = by mouth; PR = per rectum; PRN = as needed; RINV = radiation-induced nausea and vomiting; RX = prescription only; TID = three times daily.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, 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.

Systematic Reviews:

Gastroenteritis in Children

Acute enteric illness resulting in emesis is most prevalent in children younger than 3 years, then decreases in prevalence throughout childhood and becomes more common between ages 20 and 29 years.[6] Viral gastroenteritis may be caused by the Hawaii agent, rotaviruses, and adenoviruses as well as the Snow Mountain and Norwalk agents.[7] Bacterial infections with Staphylococcus aureus, Salmonella, Bacillus cereus, and Clostridium perfringens also produce nausea and vomiting, in many cases via toxins that act on the brainstem.[7] Vomiting is usually accompanied by diarrhea, and each year in the United States more than 200,000 children aged less than 5 years require hospitalization for treatment of dehydration secondary to gastroenteritis.[6] In a report published in 2003, the CDC recommended avoiding the use of antiemetics in children for treatment of gastroenteritis due to potential side effects.[6] Prochlorperazine and promethazine have a high incidence of side effects and should be avoided in patients less than 2 years.[8] The safety and efficacy of antiemetics in children with gastroenteritis has been evaluated in 3 systematic reviews.

A 2008 systematic review and meta-analysis of antiemetic agents in children with vomiting due to acute gastroenteritis evaluated emesis cessation, use of intravenous fluid for rehydration, hospital admission, and medication adverse effects.[9] Thirty articles were identified and 11 RCTs met inclusion criteria for the analysis. Antiemetics that were studied included ondansetron (n = 6), domperidone suppositories (n = 2), trimethobenzamide suppositories (n = 2), pyrilamine-pentobarbital (n = 2), metoclopramide (n = 2), dexamethasone (n = 1), and promethazine (n = 1).[9] Of note, pyrilamine-pentobarbital is no longer available in the United States and trimethobenzamide suppositories have been removed from the market due to lack of demonstrated efficacy. The authors noted the quality of studies were highly variable due to small sample sizes, low methodological quality, and inconsistent results. Data from 6 randomized, double-blind, placebo-controlled ondansetron studies including 745 subjects were robust enough to pool for a meta-analysis. The analysis of the ondansetron studies demonstrated decreased risk of further vomiting (RR 0.45; 95% CI, 0.33-0.62), reduced need for intravenous fluid (RR 0.41; 95% CI, 0.28-0.62), and decreased risk of immediate hospital admission (RR 0.52; 95% CI, 0.27-0.95).[9] Three studies noted increased diarrhea in ondansetron-treated patients. The authors concluded ondansetron decreases the risk of persistent vomiting, the use of intravenous fluids, and hospital admissions in children with vomiting due to gastroenteritis.[9] It was difficult to draw conclusions about the safety and efficacy of metoclopramide, dexamethasone, and promethazine in treating children with n/v secondary to

gastroenteritis due to poor study design. This systematic review provides moderate evidence to support the efficacy and safety of ondansetron in children with vomiting due to gastroenteritis.

A Cochrane review completed in 2009 evaluated the effectiveness and safety of antiemetics used in children for vomiting due to gastroenteritis.[10] The authors found limited data and significant heterogeneity amongst the studies. Consequently, they were not able to complete a meta-analysis of the extracted data. Four RCTs were deemed acceptable for review and provided limited evidence regarding safety and effectiveness of ondansetron and metoclopramide compared to placebo. The total population was 501 children under the age of 18 years. The primary outcome selected by the reviewers was precise time to cessation of vomiting after being administered study medication. However, none of the studies selected for inclusion assessed this outcome, so the authors provided descriptive data on the measured outcomes. Oral ondansetron in one trial demonstrated cessation of emesis for 8/12 (67%) patients within the first 4 hours and 7/12 (58%) patients in the first 24-hour period.[10] In one trial 14% of patients who received oral ondansetron vomited during oral rehydration compared to 35% in the placebo group.[10] In another trial, intravenous rehydration was required in 21.6% (ondansetron group) versus 54.5% (placebo group) which was a statistically significant difference ($p<0.001$).[10] The authors concluded that ondansetron may have reduced the amount of acute vomiting and may have reduced the number of children who required intravenous rehydration.[10] Because the evidence was weak and unreliable, the authors advocated for more research focused on the safety and efficacy of antiemetics in children with n/v secondary to gastroenteritis.

A Cochrane review compiled in 2010 updated an assessment originally published in 2005.[11] The purpose was to evaluate the efficacy and safety of antiemetics in reducing vomiting related to gastroenteritis in children and adolescents. The review included 7 RCTs and involved 1,020 patients. Four studies compared ondansetron to placebo, while 2 studies evaluated intravenous (IV) ondansetron with IV metoclopramide. One study compared rectal administration of dimenhydrinate to placebo. The authors rated the evidence as low to moderate quality with unclear to high risk of bias. There was significant heterogeneity between the trials with limited useful data. Data were pooled from 3 placebo-controlled ondansetron studies to complete a meta-analysis. The primary outcome measure was the time taken from the administration of the medication or placebo until cessation of vomiting. This primary outcome was only reported in one study. Pooled data from 3 studies comparing oral ondansetron with placebo showed a reduction in the immediate hospital admission rate (RR 0.40, 95% CI 10 to 100) and an increase in the proportion of patients with cessation of vomiting (RR 1.34, 95% CI 3 to 7).[11] Mean time to cessation of vomiting in one study was 0.34 days less with dimenhydrinate suppository compared to placebo ($p = 0.036$).[11] In one study the proportion of patients with cessation of vomiting in 24 hours was 58% with IV ondansetron, 17% with placebo and 33% in the metoclopramide group ($p = 0.039$).[11] No significant differences were noted in the rate of adverse events, although diarrhea was reported as a side effect in 4 of the ondansetron studies. The authors concluded IV ondansetron and metoclopramide reduced the number of episodes of vomiting and dimenhydrinate as a suppository reduced the duration of vomiting.[11] Oral ondansetron increased the proportion of patients who ceased vomiting and reduced the number needing IV hydration.[11] This systematic review provides moderate evidence to support the safety and efficacy of ondansetron and metoclopramide and in additional to oral rehydration therapy in pediatric gastroenteritis for patients experiencing mild to moderate dehydration.

<u>Treatment of nausea and vomiting in adults in the emergency department setting</u>

A Cochrane review published in 2015 sought to provide evidence of the efficacy and safety of antiemetic medications in the management of n/v in adults admitted to the emergency department (ED).[12] The review included 8 RCTs and involved 952 participants aged 16 years and older. Selected trials were generally of adequate quality, with 6 trials at low risk of bias, and 2 trials at high risk of bias. The trials evaluated 6 different IV antiemetics: metoclopramide (n=5), ondansetron (n=4), prochlorperazine (n=3), promethazine (n=3), tropisetron (n=1) and droperidol (n=1). Three studies compared 5 antiemetics to placebo with the same primary outcome: mean change in visual analogue scale (VAS) (0 to 100) for nausea severity from baseline to 30 minutes. Differences in mean VAS change from baseline to 30 minutes between placebo and the study drugs were noted as: metoclopramide (mean difference (MD) -5.27, 95% CI -11.33 to 0.80),

ondansetron (MD -4.32, 95% CI -11.20 to 2.56), prochlorperazine (MD -1.80, 95% CI -14.40 to 10.80), promethazine (MD -8.47, 95% CI -19.79 to 2.85) and droperidol (MD -15.8, 95% CI -26.98 to -4.62).[12] The only statistically significant change in baseline VAS to 30 minutes was for droperidol, in a single trial of 48 participants. No other drug was statistically significantly superior to placebo. The other 5 trials compared one drug to an alternative antiemetic. The evidence reported in these trials did not demonstrate superiority of any particular drug over another agent. Adverse events were generally mild and there were no reported serious adverse events. The authors concluded there is no definitive evidence to support the superiority of any one antiemetic over another or the superiority of any drug over placebo for adults admitted to the ED with n/v.[12] If a drug is considered necessary to manage n/v, choice of antiemetic may be directed by other considerations such as a patient preference and adverse-effect profile. One of the limitations of the review was the small number of clinical trials in adults treated for nausea in the ED environment.

Motion Sickness

A Cochrane review published in 2011 focused on evaluating scopolamine for preventing and treating motion sickness. This was an update of a review initially published in 2004. The authors set out to assess the effectiveness of scopolamine versus no therapy, placebo, other drugs, behavioral and complementary therapy or 2 or more therapies in combination for prevention of motion sickness.[13] Thirty-five studies were identified and 14 RCTs met inclusion criteria for the analysis. The studies were generally small in size and variable in quality with unclear risks of bias. Most of the participants had a history of motion sickness and were recruited from naval personnel on training exercises. Scopolamine was administered transdermally, orally, or intravenously. It was compared to placebo, cinnarizine, meclizine, dimenhydrinate, methscopolamine or ephedrine. The primary outcomes were prevention of onset and treatment of clinically defined motion sickness symptoms. When the data were pooled, 5 studies showed transdermal scopolamine to be superior over placebo for preventing motion sickness symptoms (risk ratio [RR] 0.48; 95% CI 0.32-0.73).[13] When compared to meclizine, scopolamine showed a decrease in the mean motion sickness score: 89% with scopolamine versus 59% with meclizine. The mean delay in onset of symptoms with scopolamine was 4.32 minutes with a (32.47% increase from baseline compared to a mean delay in symptoms of 0.58 seconds with meclizine and an 8.66% increase from baseline.[13] Adverse effects with scopolamine included drowsiness, blurred vision, dry mouth and dizziness. The small sample sizes and poor study design of the trials limited the ability to compare scopolamine to other agents. However, there was reasonable evidence to support the effectiveness of scopolamine over placebo in preventing motion sickness.

Nausea Associated with Migraine Headaches

Headache is listed among the World Health Organization's (WHO) major causes of disability with a global prevalence of 47%.[14] Migraine headaches are characterized by enhanced sensitivity of the nervous system and additional symptoms may include n/v.[15] The National Institute of Health and Care Excellence (NICE) guidelines recommend initial treatment of migraine with an oral triptan and an NSAID or an oral triptan in combination with acetaminophen.[16] If these treatments are ineffective or not tolerated, the next step is to offer an injectable or rectal preparation of metoclopramide or prochlorperazine and add an injectable NSAID such as ketorolac or nasal/injectable triptan such as sumatriptan if those therapies have not yet been tried.[16]The American Academy of Neurology (AAN) supports these recommendations and advocates for utilization of injectable, rectal or nasal routes of antiemetic administration to mitigate nausea that often accompanies migraine. [17] AAN guidelines state that nausea is one of the most aversive and disabling symptoms of migraine attack and should be treated appropriately with antiemetics.[17] Antiemetics recommended by the AAN as adjuncts in treatment of migraine include metoclopramide, prochlorperazine and 5HT3 antagonists.[17]

A Cochrane review completed in 2013 set out to determine the efficacy and tolerability of aspirin alone or in combination with an antiemetic compared to placebo or other medications in the treatment of acute migraine headaches in adults.[18] Thirteen studies with 4222 participants were included in the overall assessment.[18] The primary outcome was reduction in headache pain or pain free at 2 hours. A secondary outcome was relief of headache-associated symptoms including n/v. The studies were evaluated by the authors as medium to high quality. Aspirin 900-1000 mg with or without metoclopramide 10 mg was compared

to placebo or sumatriptan 50-100 mg in 2 studies with small numbers of patients. All medications were administered once via the oral route. The addition of metoclopramide 10 mg to aspirin 900 mg reduced nausea (RR 7.53 95% CI 4.2-13.5) and vomiting (RR 16.14 95% CI 2.3-113.05) compared with aspirin alone plus placebo in 2 studies with 417 subjects experiencing nausea and 59 subjects that vomited.[18] When metoclopramide 10mg plus aspirin 900 mg was compared to sumatriptan 100mg alone nausea was slightly reduced (RR 1.10 95% CI 0.83-1.46) in 2 studies with 410 patients. The effect on decreasing vomiting was significant in the metoclopramide/aspirin arm as compared to sumatriptan (RR 10.59 95% CI 1.43-78.64) in 67 patients. Adding metoclopramide was also effective in alleviating n/v associated with migraine headache but did not make a difference on pain relief.

Nausea Associated with Pregnancy

About 50% of women have n/v in early pregnancy, and an additional 25% have nausea alone.[19] The reported incidence of hyperemesis gravidarum is 0.3 to 1.0%. [19] This condition is characterized by persistent vomiting, weight loss of more than 5%, ketonuria, electrolyte abnormalities, and dehydration.[19] Approximately 10% of women with n/v in pregnancy require medication.[19] According to the American College of Obstetricians and Gynecologists (ACOG), treatment of n/v during pregnancy with pyridoxine or pyridoxine plus doxylamine is safe and effective and should be considered first-line therapy.[20] Several case-control and cohort studies involving more than 170,000 exposures have found this combination to be safe with regard to fetal effects.[21]

The risks of conventional antiemetics used to alleviate n/v in pregnancy have been evaluated in numerous studies. Table 4 in **Appendix 1** outlines conventional antiemetics and their safety in pregnancy as categorized by the Food and Drug Administration (FDA). A retrospective review was recently published that evaluated the risks of birth defects in children born to women who used ondansetron early in pregnancy for n/v of pregnancy or hyperemesis gravidarum.[22] Eight studies met criteria for inclusion for this analysis although data from the various studies were inconsistent and conflicting. The 3 studies of highest quality showed no increased risk of birth defects (36 malformations, 1,233 exposed compared with 141 malformations and 4,932 unexposed; with odds ratios [OR] of 1.12 (95% confidence interval [CI] 0.69–1.82), 1.3 [95% CI 1.0–1.7], and 0.95 [95% CI 0.72–1.26], respectively).[22] Two of these studies demonstrated a slightly increased risk of cardiac defects (OR 2.0 [95% CI 1.3–3.1] and 1.62 [95% CI 1.04–2.14]), but this finding was not replicated in other studies.[22] The overall risk of birth defects associated with ondansetron exposure appears to be low though there may be a small increase in the incidence of cardiac abnormalities in ondansetron-exposed babies. The authors concluded ondansetron use for n/v of pregnancy should be reserved for those women whose symptoms have not been adequately controlled by other methods.[22]

Another recent review analyzed fetal outcomes in pregnancies exposed to ondansetron to treat hyperemesis gravidarum (HG).[23] In this retrospective cohort study, data were collected on 1070 pregnancies exposed to ondansetron and compared to outcomes in 2 control groups: 771 pregnancies in women with a history of HG and no ondansetron exposure and 1555 pregnancies in women with neither a history of HG nor ondansetron exposure.[23] Ventricular septal defects were reported in 2/952 infants in the group with history of HG exposed to ondansetron and 4/1286 infants in the group with no history of HG and no exposure to ondansetron.[23] Cleft palate was reported in 1/952 live births in the group with history of HG exposed to ondansetron and 2/1286 live births in the group with no history of HG and no exposure to ondansetron.[23] Women with a history of HG who took ondansetron reported less miscarriages and terminations and higher live birth rates.[23] The overall results of this report do not support evidence of teratogenicity of ondansetron.

A retrospective cohort study to evaluate the safety of metoclopramide during the first trimester of pregnancy was published in 2009 before ondansetron became widely utilized.[24] There were 113,612 singleton births during the study period. A total of 81,703 of the infants (71.9%) were born to women in the registry, 3458 of them (4.2%) were exposed to metoclopramide during the first trimester of pregnancy.[24] Exposure to metoclopramide, as compared with no exposure to the drug, was not associated with significantly increased risks of major congenital formations (5.3% and 4.9%, respectively; odds ratio, 1.04; 95% CI,

0.89 to 1.21).[24] In this large cohort of patients, exposure to metoclopramide in the first trimester was not associated with significantly increased risks of any of several adverse outcomes.

A recent Cochrane review assessed the effectiveness and safety of all interventions for hyperemesis gravidarum (HG) in pregnancy up to 20 weeks gestation.[25] Twenty-five trials involving 2052 participants met the inclusion criteria for 18 different types of interventions including acupressure, acupuncture, ginger, IV fluids, and pharmaceutical interventions. The quality of the evidence was rated as low to very low by the authors. There was insufficient evidence to note a difference between acupuncture and metoclopramide. When metoclopramide was compared to ondansetron, no clear differences in severity of nausea measured on 10 point visual analog scale (VAS) or number of episodes of vomiting(MD 1.70; 95% CI -0.15 to 3.55 and MD -0.10; 95% CI -1.63 to 1.43, respectively) were observed.[25] However, more women taking metoclopramide complained of drowsiness and dry mouth (RR 2.40, 95% CI 1.23 to 4.69 and RR 2.38, 95% CI 1.10 to 5.11, respectively). [25] In another study, which compared promethazine to metoclopramide, promethazine appeared to cause more drowsiness (RR 0.70, 95% CI 0.56 to 0.87) and dizziness (RR 0.48, 95% CI 0.34-0.69) than metoclopramide.[25] No clear differences in quality of life were noted with promethazine compared to metoclopramide. The authors concluded there is very little high quality evidence to support one intervention over another. They recommended more research in larger controlled studies to compare efficacy and safety of the different interventions.

Postoperative Nausea and Vomiting

Nausea and vomiting can complicate 11%–73% of surgical procedures.[26] PONV is more prevalent in women, non-smokers, and younger patients.[26] PONV is also more likely in patients with a history of PONV or motion sickness.[26] Type of anesthesia administered, use of postoperative opioids, and type of surgery may also affect the risk of PONV. Conventional antiemetics recommended by the Society for Ambulatory Anesthesia for managing PONV include droperidol, scopolamine, meclizine, dimenhydrinate, and promethazine.[27]5HT3 receptor antagonists (ondansetron, dolasetron, granisetron, palonosetron) and NK-1 antagonists (aprepitant, casopitant, and rolapitant) or corticosteroids (dexamethasone and methylprednisolone) are also recommended in some cases.[27] Nabilone and dronabinol do not have proven efficacy in PONV.[27] The evidence for the safety and efficacy of conventional antiemetics in PONV has been evaluated in several systematic reviews.

A Cochrane review in 2006 assessed the efficacy of drugs in preventing PONV.[28] Seven hundred thirty-seven studies met the inclusion criteria. Sixty medications were included in the analysis and included 103,237 children and adults. Over half of the studies had some risk of bias due to unclear concealment of allocation or unclear randomization. The studies were stratified into several subgroups in order to assess if outcomes were impacted by route of administration, timing of drug administration, or administered dose. Patient demographics such as age, sex, and type of surgery were highly variable amongst all the studies. Comparisons in the studies included head-to-head studies, placebo-controlled studies and non-controlled studies. Post-operative durations studied varied from 6 to 72 hours which added more complexity to the analysis. The risk for PONV was decreased compared to placebo with cyclizine 0.67 (95 % CI 0.56 to 0.79); dimenhydrinate 0.71 (95% CI 0.59 to 0.86); dolasetron 0.72 (95% CI 0.62 to 0.83); droperidol 0.62 (95% CI 0.58 to 0.67); granisetron 0.39 (95% CI 0.31 to 0.48); metoclopramide 0.76 (95% CI 0.70 to 0.82); ondansetron 0.56 (95% CI 0.50 to 0.62); prochlorperazine 0.68 (95% CI 0.55 to 0.86); promethazine 0.46 (95% CI 0.25 to 0.82); ramosetron 0.51(95% CI 0.39 to 0.68); and tropisetron 0.72 (95% CI 0.63 to 0.82).[28] The authors concluded there is convincing evidence that cyclizine, droperidol, granisetron, metoclopramide, ondansetron, tropisetron, dolasetron and dexamethasone reduce PONV by similar amounts.[28] The authors theorized that evidence for differences in the efficacy of these 8 drugs was not convincing due to publication bias.

A meta-analysis was compiled to evaluate the efficacy and tolerability of transdermal scopolamine (TDS) in preventing PONV in adults.[29] Data from 25 randomized, placebo controlled trials were analyzed in 3298 subjects. The reviewers evaluated the following outcomes: PONV in the post-anesthesia care unit (PACU), PONV up to 48 hours after surgery, use of rescue treatment, and the prevalence of adverse effects. Study heterogeneity was reported as not significant

for nausea in the PACU. In the PACU, TDS was associated with a significantly reduced risk for PONV compared with placebo (RR = 0.77; 95% CI, 0.61–0.98; p = 0.03).[29] Significant results were also noted 24 hours after surgery as TDS application resulted in reduced risk for postoperative nausea (RR = 0.59; 95% CI, 0.48–0.73; p < 0.001), postoperative vomiting (RR = 0.68; 95% CI, 0.61–0.76; p < 0.001), and combined post-operative n/v (RR = 0.73; 95% CI, 0.60–0.88; p = 0.001).[29] Adverse effects reported with TDS therapy included dry mouth, visual disturbances, dizziness, somnolence, confusion, skin irritation, urinary retention and headache. TDS was associated with a higher prevalence of visual disturbances at 24 to 48 hours compared with placebo (RR = 3.35; 95% CI, 1.78–6.32).[29] Other adverse effects (AEs) did not show a significant association with TDS. The authors concluded TDS was associated with significant reductions in PONV but patients may also experience visual disturbances 24 to 48 hours after applying the patch.[29] This meta-analysis provides evidence for the efficacy of TDS in PONV, although some adverse effects may be experienced by patients.

A systematic review and meta-analysis compared the effectiveness of 5HT3 receptor antagonists (ondansetron, dolasetron, granisetron, and tropisetron) with traditional antiemetics (metoclopramide, perphenazine, prochlorperazine, cyclizine and droperidol) for the prevention of PONV in adults.[30] A total of 32 RCTs met the inclusion criteria and were included in the meta-analysis. Trials were stratified by surgery type, antiemetic, and induction anesthetic. The authors did not note significant heterogeneity amongst the different subgroups. Pooled data indicated a 46% reduction in the odds of PONV in the 5-HT3-treated group (OR 0.54; 95% CI 0.42-0.71; p< 0.001).[30] There was not enough evidence to pool data for the other traditional antiemetics besides metoclopramide and droperidol. 5HT3 receptor antagonists demonstrated a beneficial effect over droperidol (OR 0.61; 95% CI 0.42-0.89; p < 0.001) and metoclopramide (OR 0.44; 95% CI 0.31-0.62; p < 0.001).[30] Results in the 34 studies examining vomiting indicated a 38% reduction in the odds of vomiting in the 5-HT3-treated group (OR 0.62; 95% CI 0.48-0.81; p < 0.001).[30] The authors concluded the 5-HT3 receptor antagonists are superior to traditional antiemetic agents for the prevention of PONV.

Chemotherapy Induced Nausea and Vomiting (CINV)

Chemotherapy-induced n/v is a common treatment-related side effect that has a detrimental effect on the quality of life of patients with cancer and may lead to dose reductions in or discontinuation of chemotherapy.[31] Guidelines on antiemetic therapy in CINV that have been developed by different cancer societies show broad agreement on key principles, including: prophylaxis should be the primary goal of antiemetic therapy and should be implemented for groups of patients who have a 10% or greater risk of chemotherapy-induced emesis; the duration of prophylaxis should cover the entire risk period; oral and intravenous administration routes have the same efficacy; and the most effective antiemetic treatment is determined on the basis of chemotherapy emetogenicity, a patient's history of chemotherapy-induced emesis, and additional patient-related factors.[31]

The American Society of Clinical Oncology (ASCO) guidelines assist practitioners in determining the optimal antiemetic regimen for different clinical situations.[32] Key recommendations state:

- All patients who receive highly emetogenic chemotherapy regimens (including anthracycline plus cyclophosphamide) should be offered a 3-drug combination of a neurokinin 1 receptor antagonist, a 5- hydroxytryptamine-3 (5-HT3) receptor antagonist, and dexamethasone. The oral combination of netupitant and palonosetron (NEPA) plus dexamethasone is an additional treatment option in this setting.
- The preferred 5-HT3 receptor antagonist for patients who receive moderately emetogenic chemotherapy regimens is palonosetron; antiemetic treatment includes that agent combined with a corticosteroid.
- Both dexamethasone and a 5-HT3 receptor antagonist are recommended for patients receiving high-dose chemotherapy.
- Pediatric patients receiving either highly or moderately emetogenic chemotherapy should be treated with a 5-HT3 receptor antagonist and corticosteroids; higher weight-based dosing may be required.
- For those treated with highly emetogenic radiation therapy, a 5-HT3 receptor antagonist before each fraction and a 5-day course of dexamethasone are recommended.

- A 5-HT3 receptor antagonist before each fraction is also recommended before moderately emetogenic radiation therapy; a 5-day course of dexamethasone is optional.
- For patients who receive combination chemotherapy and radiotherapy, antiemetic therapy is dictated by the emetogenicity of chemotherapy, unless the emetic risk of radiation therapy is higher.

A Cochrane review to evaluate the effectiveness and tolerability of cannabis-based medications for CINV revealed limited evidence on this topic.[33] Twenty-three RCTs were included in the evaluation. The majority of studies were at risk of bias due to lack of allocation concealment or attrition and were rated as low to moderate quality. Most of the trials were conducted from 1975 to 1991; therefore comparisons with 5HT3 receptor antagonists were not conducted. Primary outcomes included complete control of n/v, control of vomiting or control of nausea. Nine studies compared cannabinoids as monotherapy to placebo, prochlorperazine (n=11), metoclopramide (n=2), domperidone (n=1) or chlorpromazine (n=1). In 2 studies, cannabinoids were co-administered with another antiemetic and compared to an antiemetic alone. Nabilone was evaluated in 12 RCTS and dronabinol in 11 studies. When compared to placebo, cannabinoids were more likely to reduce vomiting (RR 5.7; 95% CI 2.6 to 12.6) or reduce n/v (RR 2.9; 95% CI 1.8 to 4.7).[33] There were no differences detected between prochlorperazine and cannabinoids for n/v (nausea: RR 1.5; 95% CI 0.67 to 3.2 vomiting: RR 1.1; 95% CI 0.86 to 1.4).[33] There was not enough information to assess differences between metoclopramide, domperidone, or chlorpromazine and the cannabinoids. The authors concluded that methodological limitations limited their ability to draw definitive conclusions and that naiblone and dronabinol may be useful for treating refractory CINV.

New Formulations:
Insys Therapeutics, Inc. received FDA approval to market a new liquid formulation of dronabinol, brand name Syndros® in early July, 2016. It is indicated for the treatment of anoxrexia associated with weight loss in patients with AIDS and for nausea and vomiting associated with cancer chemotherapy in patients who fail to respond adequately to conventional antiemetic treatments. The oral solution is available as a 5 mg/ml concentrate. The recommended starting dose is 2.1mg orally twice daily, one hour before lunch and one hour before dinner. The maximum recommended daily dose is 8.4mg twice daily.[34]

References:

1. Health Evidence Review Commission Prioritized List of health services. http://www.oregon.gov/oha/herc/Pages/PrioritizedList.aspx. Accessed April 27, 2016.
2. Shapiro BJ, Lynch KL, Toochinda T, Lutnick A, Cheng HY, Kral AH. Promethazine Misuse Among Methadone Maintenance Patients and Community-Based Injection Drug Users: *Journal of Addiction Medicine*. 2013;7(2):96-101. doi:10.1097/ADM.0b013e31827f9b43.
3. Tsay ME, Procopio G, Anderson BD, Klein-Schwartz W. Abuse and Intentional Misuse of Promethazine Reported to US Poison Centers: 2002 to 2012. *J Addict Med*. 2015;9(3):233-237. doi:10.1097/ADM.0000000000000124.
4. Lexicomp Online. http://online.lexi.com/lco/action/home. Accessed May 9, 2016.
5. Micromedex Solutions | Evidence Clinical Decision Support. http://micromedex.com/. Accessed May 9, 2016.
6. Centers for Disease Control and Prevention. Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. http://www.cdc.gov/mmwr/PDF/rr/rr5216.pdf. Accessed May 18, 2016.
7. Quigley EM, Hasler WL, Parkman HP. AGA technical review on nausea and vomiting. *Gastroenterology*. 2001;120(1):263-286.
8. Manteuffel J. Use of antiemetics in children with acute gastroenteritis: Are they safe and effective? *J Emerg Trauma Shock*. 2009;2(1):3-5. doi:10.4103/0974-2700.44674.
9. DeCamp LR, Byerley JS, Doshi N, Steiner MJ. Use of antiemetic agents in acute gastroenteritis: a systematic review and meta-analysis. *Arch Pediatr Adolesc Med*. 2008;162(9):858-865. doi:10.1001/archpedi.162.9.858.
10. Alhashimi D, Al-Hashimi H, Fedorowicz Z. Antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents. [Review] [20 refs][Update in Cochrane Database Syst Rev. 2011;(9):CD005506; PMID: 21901699], [Update of Cochrane Database Syst Rev. 2006;(4):CD005506; PMID: 17054262]. *Cochrane Database of Systematic Reviews*. 2009. doi:10.1002/14651858.CD005506.pub4.
11. Fedorowicz Z, Jagannath VA, Carter B. Antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents. *Cochrane Database Syst Rev*. 2011;(9):CD005506. doi:10.1002/14651858.CD005506.pub5.
12. Furyk JS, Meek RA, Egerton-Warburton D. Drugs for the treatment of nausea and vomiting in adults in the emergency department setting. In: *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd; 2015. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010106.pub2/abstract. Accessed April 25, 2016.
13. Spinks A, Wasiak J. Scopolamine (hyoscine) for preventing and treating motion sickness. *Cochrane Database Syst Rev*. 2011;(6):CD002851. doi:10.1002/14651858.CD002851.pub4.
14. Kwon KT, Rudkin SE, Langdorf MI. Antiemetic use in pediatric gastroenteritis: a national survey of emergency physicians, pediatricians, and pediatric emergency physicians. *Clin Pediatr (Phila)*. 2002;41(9):641-652.
15. Patanwala AE, Amini R, Hays DP, Rosen P. Antiemetic therapy for nausea and vomiting in the emergency department. *J Emerg Med*. 2010;39(3):330-336. doi:10.1016/j.jemermed.2009.08.060.
16. Headaches in over 12s: diagnosis and management | Guidance and guidelines | NICE. https://www.nice.org.uk/guidance/CG150. Accessed May 6, 2016.
17. Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2000;55(6):754-762.
18. Kirthi V, Derry S, Moore RA. Aspirin with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database Syst Rev*. 2013;4:CD008041. doi:10.1002/14651858.CD008041.pub3.
19. Niebyl JR. Clinical practice. Nausea and vomiting in pregnancy. *N Engl J Med*. 2010;363(16):1544-1550. doi:10.1056/NEJMcp1003896.
20. Anonymous. Practice Bulletin No. 153: Nausea and Vomiting of Pregnancy. [Review]. *Obstetrics & Gynecology*. 2015;126(3). doi:10.1097/AOG.0000000000001048.

21. McKeigue PM, Lamm SH, Linn S, Kutcher JS. Bendectin and birth defects: I. A meta-analysis of the epidemiologic studies. *Teratology*. 1994;50(1):27-37. doi:10.1002/tera.1420500105.
22. Carstairs SD. Ondansetron Use in Pregnancy and Birth Defects: A Systematic Review. *Obstet Gynecol*. 2016;127(5):878-883. doi:10.1097/AOG.0000000000001388.
23. Fejzo MS, MacGibbon KW, Mullin PM. Ondansetron in pregnancy and risk of adverse fetal outcomes in the United States. *Reproductive Toxicology*. 2016;62:87-91. doi:10.1016/j.reprotox.2016.04.027.
24. Matok I, Gorodischer R, Koren G, Sheiner E, Wiznitzer A, Levy A. The safety of metoclopramide use in the first trimester of pregnancy. *N Engl J Med*. 2009;360(24):2528-2535. doi:10.1056/NEJMoa0807154.
25. Boelig RC, Barton SJ, Saccone G, Kelly AJ, Edwards SJ, Berghella V. Interventions for treating hyperemesis gravidarum. *Cochrane Database Syst Rev*. 2016;5:CD010607. doi:10.1002/14651858.CD010607.pub2.
26. Quinn AC, Brown JH, Wallace PG, Asbury AJ. Studies in postoperative sequelae. Nausea and vomiting--still a problem. *Anaesthesia*. 1994;49(1):62-65.
27. Gan TJ, Diemunsch P, Habib AS, et al. Consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg*. 2014;118(1):85-113. doi:10.1213/ANE.0000000000000002.
28. Carlisle JB, Stevenson CA. Drugs for preventing postoperative nausea and vomiting. [Review] [896 refs]. *Cochrane Database of Systematic Reviews*. 2006.
29. Apfel CC, Zhang K, George E, et al. Transdermal scopolamine for the prevention of postoperative nausea and vomiting: a systematic review and meta-analysis. [Review][Erratum appears in Clin Ther. 2010 Dec;32(14):2502]. *Clinical Therapeutics*. 2010;32(12):1987-2002. doi:10.1016/j.clinthera.2010.11.014.
30. Loewen PS, Marra CA, Zed PJ. 5-HT3 receptor antagonists vs traditional agents for the prophylaxis of postoperative nausea and vomiting. *Journal of Anaesthesia*. 2000;47(10):1008-1018.
31. Navari RM, Aapro M. Antiemetic Prophylaxis for Chemotherapy-Induced Nausea and Vomiting. *N Engl J Med*. 2016;374(14):1356-1367. doi:10.1056/NEJMra1515442.
32. Hesketh PJ, Bohlke K, Lyman GH, et al. Antiemetics: American Society of Clinical Oncology Focused Guideline Update. *J Clin Oncol*. 2016;34(4):381-386. doi:10.1200/JCO.2015.64.3635.
33. Smith LA, Azariah F, Lavender VTC, Stoner NS, Bettiol S. Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy. [Review]. *Cochrane Database of Systematic Reviews*. 2015. doi:10.1002/14651858.CD009464.pub2.
34. Syndros (dronabinol) Prescribing Information. Chandler, AZ: Insys Therapeutics, Inc.; July 2016.
35. By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc*. 2015;63(11):2227-2246. doi:10.1111/jgs.13702.
36. Oregon Secretary of State Archives Division. http://arcweb.sos.state.or.us/pages/rules/oars_400/oar_410/410_121.html. Accessed May 16, 2016.

Appendix 1: Specific Drug Information

Table 2. Clinical Pharmacology and Pharmacokinetics.[4,5]

Drug Name	Mechanism of Action	Absorption	Metabolism/Excretion	Pharmacokinetics (mean)
ANTIHISTAMINES				
Dimenhydrinate	Antihistamine	Well absorbed after oral or parenteral administration	Extensive hepatic metabolism Renal excretion of metabolites	•Half-life: 5-8 hours •Vd: 3-4 L/kg
Meclizine	Antihistamine	Unknown	Hepatic: CYP2D6 dominant Renal excretion: unknown	•Half-life: 5- 6 hours
CANNABINOID AGONISTS				
Dronabinol	Cannabinoid Agonist	Oral bioavailability = 90-95% absorbed, only 10-20% reaches circulation due to extensive first pass metabolism	Extensive hepatic metabolism Renal excretion: 10-15%	•Half-life: 19-36 hours •Vd: 10 L/kg (highly lipid soluble)
Nabilone	Cannabinoid Agonist	Oral bioavailability = 95.6-100%	Extensive hepatic metabolism Renal excretion = 20-24%	•Half-life: 2 hours (parent) 35 hours (metabolites) •Vd: 12.5 L/kg
BENZAMIDES				
Metoclopramide	Benzamide • Cholinomimetic • Dopamine antagonist • Serotonin antagonist (at higher doses)	Oral bioavailability = 80%	Minimal hepatic excretion Renal Excretion = 75-85%	•Half-life: 5-6 hours •Vd: 3.5 L/kg
Trimethobenzamide	Benzamide • Histamine Antagonist	Oral bioavailability = 100%	Renal excretion: 30-50%	•Half-life: 7-9 hours
PHENOTHIAZINES				
Prochlorperazine	Phenothiazine • Anticholinergic • Dopamine antagonist	Oral bioavailability = 12.5%	Extensive hepatic metabolism	•Half-life: 7-9 hours •Vd: 12.9-17.7 L/kg
Promethazine	Phenothiazine • Anticholinergic • Antihistamine • Dopamine antagonist	Well absorbed orally	Hepatic	•Half-life: 9 hours
ANTICHOLINERGIC				
Scopolamine	Anticholinergic	Well absorbed percutaneously	Extensive hepatic metabolism Renal < 10%	•Half-life: 9.5 hours

Use in Specific Populations:

Potentially Inappropriate Medication in Older Adults (AGS Beers Criteria) [35]

Dimenhydrinate
Meclizine
Metoclopramide
Prochlorperazine
Promethazine
Scopolamine

Pediatric Warnings [4,5]

Dimenhydrinate: safety in children < 2 years of age not established – may cause excitation in young children
Meclizine: safety and efficacy not established in children < 12 years of age
Prochlorperazine: safety and efficacy not established in children < 2 years of age or < 9 kg
Promethazine: use is contraindicated in children < 2 years of age due to the risk of fatal respiratory depression

Drug Safety:

Black Boxed Warnings

Metoclopramide: May cause tardive dyskinesia a serious movement disorder that is often irreversible. Risk of developing tardive dyskinesia increases with duration of treatment and total cumulative dose. There is no known treatment for tardive dyskinesia, although symptoms may lessen or resolve after metoclopramide discontinuation. Prolonged treatment with metoclopramide (greater than 12 weeks) should be avoided in all but rare cases where therapeutic benefit outweighs the risks.[5]

Prochlorperazine injection: Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared with placebo. Although the causes of death in the clinical trials were varied, most deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. It is unclear from these studies to what extent the mortality findings may be attributed to the antipsychotic drug as opposed to the patient characteristics. Prochlorperazine edisylate injection is not approved for the treatment of patients with dementia-related psychosis.[5]

Promethazine injection: Promethazine hydrochloride injection should not be used in pediatric patients less than 2 years old because of the potential for fatal respiratory depression. Respiratory depression, including fatalities, have been reported with use of promethazine in pediatric patients less than 2 years old in post-marketing experience. Exercise caution when administering promethazine hydrochloride injection to pediatric patients 2 years or older. Regardless of the administration route, promethazine hydrochloride injection can cause severe chemical irritation and damage to the tissue. Adverse reactions include burning, pain, thrombophlebitis, tissue necrosis, and gangrene, requiring surgical intervention, skin graft and/or amputation in some cases. Due to the risks of IV administration, the preferred route of administration is deep IM injection. Subcutaneous injection is contraindicated.[5]

Table 3. Summary of Warnings and Precautions.[4,5]

Warning/Precaution	Dimenhydrinate	Meclizine	Dronabinol	Nabilone	Metoclopramide	Prochlorperazine	Promethazine	Trimethobenzamide	Scopolamine
Controlled substance due to abuse potential			X	X					
CV Disease	X		X	X	X	X	X		X
Seizures	X		X		X		X	X	X
Hepatic Impairment	X	X							
CNS depression	X	X	X	X	X	X	X		X
Glaucoma	X	X				X			X
Respiratory Disease	X	X							X
Prostatic Hypertrophy	X	X							X
Extrapyramidal reactions					X	X	X	X	
Neuroleptic Malignant Syndrome					X	X	X		
Dementia Related Psychosis						X			
Peptic Ulcer	X	X							X
Hyperthyroidism	X								
Renal Impairment					X			X	X
Psychiatric Disorders			X	X	X				
Hepatic Impairment								X	X

Table 4. Antiemetics and their safety risk in pregnancy.[15]

Medication	**FDA Category***
Vitamin B6 (Pyridoxine)	A
Vitamin B6-Doxylamine combination	A
Doxylamine	A
Diphenhydramine	B
Meclizine	B
Dimenhydrinate	B
Promethazine	C
Prochlorperazine	C
Trimethobenzamide	C
Metoclopramide	B
Droperidol	C
Ondansetron	B
Ginger	C

*FDA categories: A: controlled studies show no risk, B: no evidence of risk in humans, C: risk cannot be ruled out, D: positive evidence of risk, X: contraindicated in pregnancy

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to May Week 1 2016, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations May 10, 2016
1 gastroenteritis {No Related Terms} 9320
2 nausea {No Related Terms} 11863
3 vertigo {No Related Terms} 7424
4 motion sickness {No Related Terms} 1281
5 post-operative nausea and vomiting 206
6 pregnancy and nausea {No Related Terms} 10977
7 chemotherapy induced nausea {No Related Terms} 10108
8 1 or 2 or 3 or 4 or 5 or 6 or 7 41050
9 8 no related term s 26609
10 limit 9 to humans 17818
11 dimenhydrinate {No Related Terms} 198
12 dronabinol {No Related Terms} 3027
13 meclizine {No Related Terms} 73
14 metoclopramide {No Related Terms} 2097
15 nabilone {No Related Terms} 112
16 prochlorperazine {No Related Terms} 322
17 promethazine {No Related Terms} 837
18 scopolamine patch {No Related Terms} 5645
19 trimethobenzamide {No Related Terms} 21
20 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 12024
21 limit 20 to (humans and (clinical study or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or meta analysis or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 2610
22 8 and 20 948
23 limit 22 to (full text and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or meta analysis or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 317

Appendix 3: Utilization of Conventional Antiemetics in the Medicaid Fee For Service Population

Table 5. Antiemetic Indications and OHP Funding.[1]

Diagnosis	OHP Funded Line	Funding Status
Pregnancy-related N/V	1	Funded
Enteritis	32	Funded
Enteric Infection/Food Poisoning	150	Funded
Cancer	28, 116,117,137,161,195,204,205,213, 215, 219, 220, 222,243,263,264,266,267,275,280, 291,292,299,319, 320, 321, 334, 439, 440	Funded
Post-Operative N/V	75	Funded
Migraine Headache	415	Funded
Motion Sickness/Vertigo	515	Not Funded
Gastroesophageal Reflux	516	Not Funded
Persistent Vomiting	531	Not Funded
Gastroparesis*	531	Not Funded
Irritable Bowel Syndrome	531	Not Funded
Noninfectious Gastroenteritis	555	Not Funded

*If gastroparesis is due to diabetes, it is funded condition due to the comorbidity rule as described in Oregon Administrative Rule (OAR) 410-121-0040[36]

Table 6. Fee For Service Pharmacy Claims for Conventional Antiemetics: October 2014 to September 2015.

Drug Name	Drug Form	Patient Count	Claim Count	Amount Paid
Compro	Supp.rect	2	7	$624
Dimenhydrinate	Tablet	1	1	$6
Driminate	Tablet	2	3	$29
Dronabinol	Capsule	24	66	$17,761
Formula EM	Solution	1	1	$13
Marinol	Capsule	1	1	$14
Meclizine	Tab chew	35	45	$399
Meclizine	Tablet	372	630	$9,315
Metoclopramide	Solution	31	143	$1,492
Metoclopramide	Tablet	456	831	$7,559
Metoclopramide	Vial	3	3	$27
Motion sickness	Tablet	1	1	$10
Phenadoz	Supp.rect	109	139	$8,428
Prochlorperazine	Supp.rect	24	30	$2,574
Prochlorperazine maleate	Tablet	381	580	$5,287
Promethazine	Ampul	4	5	$62
Promethazine	Supp.rect	21	29	$2,264
Promethazine	Syrup	41	53	$496
Promethazine	Tablet	2,486	4,259	$41,976
Promethazine	Vial	10	13	$191
Promethegan	Supp.rect	146	191	$19,331
Transderm-scop	Patch td 3	107	193	$15,318
Travel sickness	Tab chew	71	139	$1,293
Trimethobenzamide	Capsule	1	1	$29
Totals		4,330	7,364	$134,500

Table 7. Number of patients started on antiemetic therapy from 10/1/14 to 9/30/15 in the Medicaid FFS population.

Total Patients Meeting Criteria	**2,212**	
Funded	**Patient Count**	**%**
Enteritis	3	0.1%
Enteric Infection/Food Poisoning	2	0.1%
Cancer	161	7.3%
Post Op N/V	548	24.8%
Total Unique Funded:	672	30.4%
Not Funded	**Patient Count**	**%**
Motion Sickness	5	0.2%
Vertigo	125	5.7%
Gastroesophogeal Reflux	87	3.9%
Gastroparesis	11	0.5%
Irritable Bowel Syndrome	10	0.5%
Noninfectuous Gastroenteritis	37	1.7%
Total Unique Not Funded:	262	11.8%
Patients with none of the above:	1,278	57.8%

Table 8. Antiemetic claims in patients with concurrent claims for an opioid and a recent history (past 18 months) of substance abuse.

Category	#	%
Received at least one Antiemetic in the last 6 months (FFS or MCO - Jan-Jun 2016)	1,960	100%
Received at least one opioid and one antiemetic in the last 6 months (FFS or MCO - Jan-Jun 2016)	1,075	55%
Received at least one opioid and one antiemetic in the last 6 months and has a recent history (18 months Jan-15 through Jun-16) of substance abuse	336	17%
Received at least one antiemetic but no opioids in the last 6 months and has a recent history (18 months Jan-15 through Jun-16) of substance abuse	168	9%

Antiemetics

Goal(s):

- Promote use of preferred antiemetics.
- Restrict use of antiemetics for OHP-funded conditions in which medical evidence supports use.
- Restrict inappropriate chronic use.
- For patients receiving chemotherapy or radiation, approve a quantity sufficient for 3 days beyond the duration of treatment.

Length of Authorization:

- Up to 6 months, or variable depending on chemotherapy

Requires PA:

- Non-preferred drugs
- Preferred drugs when quantity limit exceeded (Table 1)

Table 1. Quantity Limits for Antiemetic Drugs.

Drug	Trade Name	Dose Limits
5-HT3 Receptor Antagonists		
Ondansetron	Zofran, Zuplenz, generic formulations	12 doses/ 7 days
Dolasetron	Anzemet	1 dose/ 7 days
Granisetron	Sancuso transdermal Generic oral	1 patch / 7 days 1 dose/ 7 days
Substance P/neurokinin 1 (NK1) Receptor Antagonists		
Aprepitant	Emend	3 doses/ 7 days
Rolapitant	Varubi	1 dose/ 7 days
Substance P/neurokinin 1 (NK1) Receptor Antagonists and 5-HT3 Receptor Antagonists Combinations		
Netupitant/palonosetron	Akynzeo	1 dose/ 7 days
Cannabinoid Receptor Agonist		
Dronabinol	Marinol	2.5 mg and 5 mg = 3 doses/day 10 mg = 2 doses/day

Covered Alternatives:

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

Approval Criteria		
1. What is the diagnosis being treated?	Record ICD10 Code.	
2. Is the requested drug preferred?	**Yes:** Go to #4	**No:** Go to #3
3. Will the prescriber consider a change to the preferred product? Note: • Preferred products do not require a PA unless they exceed dose limits in **Table 1**. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class and dose limits. If dose exceeds limits, go to #4.	**No:** Go to #4
4. Is the request for doxylamine/pyridoxine (Diclegis®) for pregnancy-related nausea or vomiting?	**Yes:** Go to #5	**No:** Go to #6
5. Has the patient failed a trial of pyridoxine? Note: • Preferred pyridoxine products do not require a PA and are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics Committee.	**Yes:** Approve for up to 3 months	**No:** Pass to RPh; deny and recommend a trial of pyridoxine.
6. Is the request for dronabinol?	**Yes:** Go to #7	**No:** Go to #8
7. Does the patient have anorexia associated with HIV/AIDS?	**Yes:** Approve for up to 6 months. Apply quantity limit for drugs listed in **Table 1**.	**No:** Go to #8
8. Does the patient have a cancer diagnosis AND receiving chemotherapy or radiation?	**Yes:** Approve for 3 days beyond length of chemotherapy regimen or radiation (not subject to quantity limits)	**No:** Go to #9

9. Does patient have refractory nausea/vomiting that has resulted in hospitalizations or ED visits in the past 6 months?	**Yes:** Approve for up to 6 months (not subject to quantity limits)	**No:** Go to #10
10. Has the patient tried and failed, or have contraindications, to at least 2 preferred antiemetics?	**Yes:** Approve for up to 6 months. Apply quantity limit for drugs listed in **Table 1**.	**No:** Pass to RPh. Go to #11
11. RPh only: All other indications need to be evaluated as to whether they are funded under the Oregon Health Plan. [ ] Funded: Deny; medical appropriateness. Must trial at least 2 preferred antiemetics. [ ] Non-funded: Deny; not funded by the OHP.		

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

Antiemetics

Goal(s):

- Promote use of preferred drugs.
- Restrict use of costly antiemetic agents for appropriate indications.
- Restrict inappropriate chronic use (>3 days per week).
- For patients receiving chemotherapy or radiation, approve a quantity sufficient for 3 days beyond the duration of treatment.

Length of Authorization:

- Up to 6 months, or variable depending on chemotherapy (criteria specific)

Requires PA:

- Non-preferred drugs will be subject to PA criteria and quantity limits (Table 1)
- Preferred drugs will deny only when quantity limit exceeded

Table 1. Quantity Limits for Antiemetic Drugs.

Drug	Trade Name	Dose Limits
5-HT3 Receptor Antagonists		
Ondansetron	Zofran, Zuplenz, generic formulations	12 doses/ 7 days
Dolasetron	Anzemet	1 dose/ 7 days
Granisetron	Sancuso transdermal Generic oral	1 patch / 7 days 1 dose/ 7 days
Substance P/neurokinin 1 (NK1) Receptor Antagonists		
Aprepitant	Emend	3 doses/ 7 days
Rolapitant	Varubi	1 dose/ 7 days
Substance P/neurokinin 1 (NK1) Receptor Antagonists and 5-HT3 Receptor Antagonists Combinations		
Netupitant/palonosetron	Akynzeo	1 dose/ 7 days

Covered Alternatives:

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

Approval Criteria		
1. What is the diagnosis being treated?	Record ICD10 Code.	
2. Is the requested drug preferred?	**Yes:** Go to #4	**No:** Go to #3
3. Will the prescriber consider a change to the preferred product? Message: • Preferred products do not require a PA unless they exceed dose limits in table 1. • Preferred products are reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class and dose limits. If dose exceeds limits, continue to #4.	**No:** Go to #4
4. Is the request for doxylamine/pyridoxine (Diclegis®) for pregnancy-related nausea or vomiting?	**Yes:** Go to #5	**No:** Go to #6
5. Has the patient failed a trial of pyridoxine? Message: • Preferred vitamin B products do not require a PA and are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Approve for up to 3 months	**No:** Pass to RPh; deny and recommend a trial of pyridoxine.
6. Does the patient have a cancer diagnosis and receiving chemotherapy or radiation?	**Yes:** Approve for 3 days beyond length of chemotherapy regimen or radiation (not subject to dose limits above)	**No:** Go to #7
7. Does patient have refractory nausea that has resulted in hospitalizations or ED visits?	**Yes:** Approve for up to 6 months	**No:** Go to #8
8. RPh only: All other indications need to be evaluated as to whether they are funded under the Oregon Health Plan. [ ] Funded: Deny for medical appropriateness		

[ ] Non-funded: Deny; not funded by the OHP

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

Dronabinol (Marinol®)

Goal(s):

- Cover drugs only when used for covered OHP diagnoses, and restrict use to instances where medical evidence supports use (e.g. Nausea associated with chemotherapy).There is limited medical evidence supporting the use of dronabinol for many conditions.

Length of Authorization:

6 months to lifetime (criteria specific)

Requires PA:

- Dronabinol (Marinol®)

Quantity Limits:

- 2.5mg & 5 mg = 3 units per day
- 10mg = 2 units per day

Apply ONLY to HIV/AIDS related anorexia and Non-Oncology related antiemetic use. No quantity limits apply for Oncology (cancer) related antiemetic use.

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org
- Metoclopramide (Reglan®)
- Prochlorperazine (Compazine®)
- Promethazine (Phenergan®)
- 5 HT3 antagonists (Zofran®, Anzemet®, or Kytril®) – authorized for >3 days

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

<table>
<tr><th colspan="3">Approval Criteria</th></tr>
<tr><td>2. Does client have diagnosis of anorexia associated with AIDS? HIV?</td><td>Yes: Approve for lifetime (until 12-31-2036). Apply quantity limit (Anorexia associated with AIDS/HIV)</td><td>No: Go to #3.</td></tr>
<tr><td>3. Does client have current diagnosis of cancer AND receiving chemotherapy or radiation therapy?</td><td>Yes: Approve for length of chemo or radiation therapy. No quantity limit. (Chemotherapy or Radiation, whichever is applicable)</td><td>No: Go to #4.</td></tr>
<tr><td>4. Does client have refractory nausea that would require hospitalization or ER visits?</td><td>Yes: Go to #5.</td><td>No: Go to #7.</td></tr>
<tr><td>5. Has client tried two medications listed below?
<table><tr><th>Generic Name</th><th>Brand Name</th></tr><tr><td>Metoclopramide</td><td>Reglan®</td></tr><tr><td>Prochlorperazine</td><td>Compazine®</td></tr><tr><td>Promethazine</td><td>Phenergan®</td></tr></table>
5 HT3 drugs - Zofran®, Anzemet®, Kytril®</td><td>Yes: Approve for up to six months. Apply quantity limit (Refractory Nausea With Failure of Alternative Meds)</td><td>No: Go to #6.</td></tr>
<tr><td>6. Does client have contraindications, such as allergies, or other reasons they CANNOT use these anti-emetics? Document reason.</td><td>Yes: Approve for up to six months. Apply quantity limit (Refractory Nausea With Contraindication of Alternative Meds)</td><td>No: Go to #7.</td></tr>
<tr><td>7. Does client have ONE of more of following diagnosis? Cancer associated anorexia, dystonic disorders, glaucoma, migraine, multiple sclerosis, pain.</td><td>Yes: Pass to RPH; Deny, (Medical Appropriateness)</td><td>No: Pass to RPH; Go to #8.</td></tr>
</table>

Approval Criteria		
8. RPH only All other indications need to be evaluated to see if they are above or below the line	Above: Deny, (Medical Appropriateness)	Below: Deny, (Not-Covered by the OHP)

P&T / DUR Review: *2/23/06, 2/24/04, 2/11/03*
Implementation: *10/15, 7/1/06, 5/31/05*

Drug Use Research & Management Program
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Class Update with New Drug Evaluation: Hormone Replacement Therapy (non-contraceptive uses)

Date of Review: January 2017
Generic Name: Ospemifene

End Date of Literature Search: September 2016
Brand Name (Manufacturer): Osphena (Shionogi, Inc)
Dossier Received: Yes

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

Purpose for Class Update:
Evidence for the comparative effectiveness of estrogen preparations was last reviewed by the Oregon Pharmacy & Therapeutic Committee (P&T) in November 2014. A comprehensive review of progestin products has never been completed. This review examines new comparative evidence of estrogen replacement therapy published since 2014 and provides a comprehensive evaluation of evidence published since 2010 for the comparative efficacy of progestin preparations. Ospemifene, a new selective estrogen receptor modulator (SERM), for the treatment of vaginal symptoms associated with menopause is also reviewed.

Research Questions:
1. Is there any new comparative evidence assessing efficacy of hormone replacement therapy (HRT; including estrogens, progestins, estrogen/progestin combinations, estrogen-bazedoxifene combinations, and estrogen-androgen combinations) in the treatment of symptoms associated with menopause?
2. Is there any new comparative evidence on the long-term benefits and harms of HRT?
3. Are there subpopulations of adults (specifically > 60 years of age, > 10 years since menopause, with or without a uterus) for which HRT for menopause is more effective or associated with more long-term adverse effects?
4. What is the evidence for efficacy and safety of ospemifene for the treatment of vaginal dryness and dyspareunia associated with menopause?
5. What is the comparative evidence assessing efficacy of progestin agents and formulations for treatment of endometrial conditions (including endometriosis, endometrial cancer, and endometrial hyperplasia), abnormal uterine bleeding, and prevention of preterm labor?

Conclusions:
Efficacy of HRT and ospemifene for menopause symptoms
- Estrogens are the most effective agents at relieving common symptoms associated with menopause.[1] They can be utilized as monotherapy or in combination with other hormone products.
    - No meaningful differences were observed between estrogen dose (moderate strength of evidence) or route of administration (high strength of evidence) for the treatment of vasomotor symptoms.[1]
    - There is moderate strength evidence demonstrating no difference in pain during intercourse or quality of life between estrogen formulations.[1]

- There is moderate strength evidence demonstrating no difference in sleep between low or standard dose estrogens.[1]
- There is insufficient evidence comparing efficacy of different estrogen doses or formulations in treatment of psychological or urogenital symptoms.[1]

- There is insufficient evidence to evaluate differences in efficacy of ospemifene versus other hormone therapies for improvement of menopause symptoms. There is low strength evidence that ospemifene improves urogenital symptoms of dyspareunia with (mean difference [MD] of 0.51 to 0.36 points compared to placebo).[2,3] Symptoms were measured on a 4-point severity scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). The minimum clinically important difference with this scale has not been established.
- There is insufficient evidence evaluating the efficacy of progestin only products for the treatment of menopause symptoms, and there is no new comparative evidence evaluating safety or efficacy of combination estrogen/bazedoxifene for the treatment of menopause symptoms.
- There is insufficient evidence to evaluate differences in efficacy of estrogen products in specific populations based on age, symptom severity, time since menopause and uterine status.

Long-term safety of HRT

- Both estrogen only and estrogen/progestin combinations increase risk of gallbladder disease, venous thromboembolism (VTE), and stroke (high strength of evidence) and decrease risk for osteoporotic fractures (moderate strength of evidence).[1]
- Breast cancer risk is increased with estrogen/progestin combinations (high strength of evidence), but may decrease with estrogen alone (low strength of evidence with inconsistent results).[1]
- There is low strength of evidence that estrogen/progestin combinations decrease risk of colorectal cancer but moderate strength of evidence that estrogen alone has no effect.[1]
- Risk for coronary heart disease is increased with estrogen/progestin combinations but is not affected by estrogen alone (moderate strength of evidence).[1]
- There is moderate strength evidence that HRT is not associated with increased risk of diabetes.[4,5]
- There is low strength evidence from direct and indirect comparisons of observational studies that oral HRT (with or without progestins) is associated with greater risk of VTE compared to transdermal formulations.[1,4]
- There is insufficient evidence to evaluate differences in other long-term adverse effects between individual products, formulations, or doses of estrogen only or estrogen/progestin combinations. There is also insufficient evidence to evaluate the long-term safety of ospemifene.
- Low quality evidence from systematic reviews with inconsistent results which demonstrates that risk of myocardial infarction (MI), cardiovascular disease, or cardiovascular mortality may not increase in women less than 65 years of age treated with estrogen or combined estrogen/progestin formulations.[4]
- There is low quality evidence, from systematic reviews limited by population size and quality of trials, that use of HRT does not increase the risk of endometrial cancer in patients with a prior history of surgery for endometrial or ovarian cancer.[6,7]

Efficacy and safety of progestins for other indications

- There is low quality evidence that use of progestins does not improve symptoms of pain or fertility outcomes associated with endometriosis.[8] However, despite limited evidence, guidelines recommend the use of progestins for the treatment of pain associated with endometriosis.[9,10] There is insufficient evidence to determine differences between formulations.
- There is low quality evidence from multiple systematic reviews with inconsistent results that use of a levonorgestrel intrauterine device (IUD) in women with heavy uterine bleeding may be associated with greater reduction in bleeding compared to oral therapy.[11-13] There is insufficient evidence to assess efficacy of other progestin products or formulations.

- There is moderate quality evidence from systematic reviews of observational studies that use of progestins results in initial cancer regression in approximately 70% of women with endometrial carcinoma or atypical complex endometrial hyperplasia.[14,15] There is high quality evidence that use of progestins as fertility-sparing treatment in women in this population results in significant relapse rates (range 20.1 to 40.6%) upon long-term follow-up.[14,15] There is insufficient evidence comparing safety or efficacy of different progestin formulations in the treatment of endometrial carcinoma or atypical complex endometrial hyperplasia.
- There is moderate quality evidence that use of progestins in high risk women with a short cervix (<25 mm) and history of preterm birth is associated with decreased perinatal mortality and preterm birth at 34 or 37 weeks.[16-19] No improvement in clinical neonatal outcomes was observed in women without a history of preterm birth. There is low quality evidence based on direct and indirect comparisons demonstrating benefit with both vaginal and systemic formulations.[16,20]

Recommendations:

- Combine progestin agents into one PDL class and designate at least one preferred product for FDA-approved indications funded by the Oregon Health Plan (endometriosis, endometrial cancer, endometrial hyperplasia, abnormal bleeding disorders, and prevention of preterm birth) based utilization and comparative drug costs in the executive session.
- Evaluate comparative costs of oral, vaginal and topical estrogen and estrogen/progestin combination products in the executive session.
- Restrict coverage of ospemifene subject to prior authorization. Dyspareunia is a non-funded condition and there is insufficient evidence that other symptoms of vaginal atrophy improve with treatment.
- No changes to current clinical prior authorization (**Appendix 4**) recommended.

Previous Conclusions:

- There is high quality evidence that estrogens are the most effective agents at relieving common symptoms associated with menopause, including vasomotor symptoms and quality of life, with no significant differences between doses or mode of administration. There is high strength of evidence that vaginal estrogen reduces pain during intercourse and insufficient evidence for oral estrogen.
- There is no new significant comparative evidence on the efficacy or safety of hormone replacement therapy medications.
- Conjugated estrogens/bazedoxifene (CE/BZA; DUAVEE) has not been compared with current therapies for postmenopausal vasomotor symptoms. Only one phase 3 poor quality trial (SMART 2) and one supportive poor quality sub-study (SMART 1) comparing CE/BZA with placebo provide low quality evidence.
- CE/BZA significantly reduced the number and severity of hot flushes (mean difference in the daily number of moderate and severe hot flushes between CE/BZA and placebo was –2.71 in SMART 2 and -6.29 in sub-study SMART 1).
- Evidence that CE/BZA improves health-related quality of life (HRQOL) is insufficient. One combined analysis provides low quality evidence that CE/BZA versus placebo results in a meaningful change in vasomotor functioning scores.
- The poor quality SMART 5 trial provides low quality evidence CE/BZA significantly increases lumbar spine and total hip bone mineral density (BMD) compared with placebo (placebo subtracted difference 1.51% for the lumbar spine and 1.21% for the total hip). However, the researchers observed no statistically significant difference between the CE/MPA subgroup and CE/BZA and did not evaluate fracture risk.
- Clinical trials provide low quality evidence for the CE/BZA indications for treatment of vasomotor symptoms and prevention of osteoporosis. The incidences of all-cause mortality, serious adverse events, venous thromboembolism (VTE), and endometrial hyperplasia or endometrial malignancy in patients taking CE/BZA were similar to placebo. However, the adverse effects associated with use in a general, menopausal population remain unexplored. The potential

implications of discontinuing CE/BZA, such as the rapid bone loss associated with CE-alone use, are unclear. CE/BZA comes with the CE-related risk of VTE and ischemic stroke, and the benefits of oral hormone therapy are more likely to outweigh the risks before age 60 or within 10 years of menopause.

Previous Recommendations:

- There is no further review or research needed for estrogen replacement therapy at this time.
- Make CE/BZA non-preferred and subject to clinical prior authorization criteria due to insufficient evidence comparing it with currently available therapies and low quality evidence of efficacy compared with placebo.

Background:

Hormone replacement therapy (HRT) refers to the use of estrogen alone or in combination with progestin products. The most common indication for estrogen therapy is for the treatment of menopausal symptoms, though estrogens also have FDA indications for palliative treatment of metastatic breast cancer, metastatic prostate cancer, and postmenopausal osteoporosis.[21] They can also be used off-label as cross-sex hormone replacement in gender dysphoria (see Class Review, Nov 2015).[22]

Symptoms of menopause result from a decrease in estrogen and progesterone levels leading to more sensitive body temperature regulation as well as decreased vaginal blood flow and secretions.[23] Up to 75% of postmenopausal women experience vasomotor symptoms (hot flashes, night sweats or sleep disturbances) and up to 50% may experience urogenital symptoms (including sexual dysfunction, vaginal dryness, discharge, itching, and dyspareunia or pain with sexual intercourse).[4] Vasomotor symptoms typically start within 1 year after the last menstrual period and resolve spontaneously in the majority of women after 5 years though they can last for longer than 10 years.[23]

For mild menopause symptoms, lifestyle modifications including diet, exercise, environmental temperature regulation, and vaginal lubricants may be sufficient to manage symptoms. For more severe menopause symptoms, first-line medication management includes HRT with an estrogen product. Preparations of estrogen include vaginal, transdermal, and oral formulations. A list of available estrogen products and their PDL status is available in Appendix 1. Potential long-term risks of estrogen include increased risk of cardiovascular complications and breast cancer. Caution is advised for patients with predisposing risk factors for these conditions.[4,24] Estrogens may also increase risk for endometrial cancer in women with a uterus.[25] Guidelines recommend concurrent use of a progestin in these women to decrease risk of endometrial cancer; all estrogens carry an FDA warning for endometrial cancer associated with estrogen only therapy.[4,24] For women who have contraindications to or are not willing to use hormone products, additional second-line treatment options for symptoms of menopause include selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), gabapentin, pregabalin, ospemifene or clonidine. Long-term benefits of HRT include decreased risk of osteoporotic fractures and colorectal cancer, but HRT is not recommended for prevention of long-term conditions such as osteoporosis as the potential risks may outweigh any benefits.[4]

Ospemifene is a new selective estrogen receptor modulator (SERM) approved in 2013 for the treatment of moderate to severe dyspareunia in women with vulvar and vaginal atrophy as a result of menopause. Vaginal atrophy falls within the covered conditions on the prioritized list, but dyspareunia is not a covered condition. Ospemifene acts as an antagonist in the endometrium and as an agonist in the uterus, bone, and breast tissue. Ospemifene was approved on the basis of 2 phase 3 clinical trials supporting efficacy in the treatment of moderate to severe dyspareunia. Supporting data were provided from other phase 2 and 3 trials. The phase 3 studies included 1,745 patients aged 40-80 years with menopause and vulvovaginal symptoms that were randomized to ospemifene (either 30 mg or 60 mg) or placebo with follow-up at 12 weeks.[26-28] Extension studies to determine safety up to 1 year were also conducted. In efficacy trials, all participants were allowed to utilize vaginal lubricants as needed. Outcomes for these trials included vaginal pH, maturation index, and improvement in

symptoms of dyspareunia and vaginal dryness. Vaginal pH has been used to determine stage of menopause with a pH less than 4.5 associated with low estrogen levels indicative of perimenopause or menopause.[29,30] Use of vaginal maturation index, measured by a decrease in superficial cells and an increase in parabasal cells upon vaginal smear, has also been used for determining stage of menopause. This method involves obtaining cells from the vaginal wall to determine the percentages of parabasal, intermediate and superficial cells. A higher percentage of parabasal cells has been documented in postmenopausal women compared to premenopausal women.[23] However, vaginal pH and maturation index are surrogate endpoints which have not been correlated with symptom improvement in postmenopausal women, and a minimum clinically important difference has not been established in the literature. Assessment of the most bothersome moderate to severe symptom (either vaginal dryness or dyspareunia) was measured on a 4-point Likert scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). There is currently no consistently used scale for assessment of menopause symptoms, and the minimal clinical important difference with the use of a 4-point severity scale has not been established. Important clinical outcomes would include improvement in symptoms and rates of long-term adverse events. Additional studies to establish efficacy in patients with other genitourinary symptoms associated menopause are ongoing.[31]

Progestin products are recommended in combination with estrogen treatment to decrease risk of endometrial cancer in women with a uterus utilizing HRT for menopause symptoms. Progestins are also FDA approved for use in contraception, prevention of preterm labor and a wide variety of endometrial conditions including endometrial carcinoma, endometrial hyperplasia, endometriosis, and abnormal uterine bleeding. Indications are specific to the agent and formulation (see Table 1). Currently, medroxyprogesterone intramuscular (IM) or subcutaneous (SC) injections are the only progestin products that have indications for both contraception and endometrial disorders. Hydroxyprogesterone caproate injection is the only product FDA approved for prevention of preterm labor, though other progestins may be used off-label for this indication. Efficacy of hydroxyprogesterone caproate for use in preterm labor was previously reviewed by the P&T Committee in 2013.[32]

Because progestins induce development of the secretory endometrium and block follicular maturation and ovulation, they are commonly used for endometriosis and regulation of abnormal uterine bleeding.[21] Endometriosis is a condition where endometrial tissue located outside the uterus causes pelvic pain and infertility.[21] When used for the treatment of endometriosis, progestins are thought to improve pain by decreasing proliferation of endometrial tissue outside of the uterus.[33] Guidelines recommend progestins as an option for the treatment of pain associated with endometriosis but note that they do not improve fertility in patients with endometriosis.[9,10] Agents approved by the FDA for treatment of endometriosis include medroxyprogesterone acetate subcutaneous injection and norethindrone acetate. Abnormal uterine bleeding is defined as changes in the volume, regularity, frequency or duration of menstrual periods.[34] Typical duration of menstrual periods is 3 to 8 days with consistent cycles every 24 to 38 days.[34] Diagnosis of abnormal uterine bleeding is typically patient specific and evaluates impact of the woman's quality of life.[34] Studies examining efficacy of medications utilize several methods to evaluate the impact on menstrual bleeding. Methods to measure the volume of blood lost per cycle include the use of the pictorial bleeding assessment chart (PBAC) scores or the alkaline haematin method. The alkaline haematin method utilizes spectroscopy to estimate the amount of alkaline haematin in blood samples which can be correlated accurately to the volume of blood in the sample.[35] PBAC score utilizes the subjective patient assessment of bleeding intensity and number of sanitary items to evaluate volume of blood loss.[36] Validity of PBAC scores has been evaluated in several studies which suggest that, due to the subjective nature of the test, inter-patient variability may be high.[36,37] However, PBAC scores may have some utilization in determination of change in blood loss over time as their documented intra-patient variability is low.[36] Clinically important outcomes for abnormal uterine bleeding include symptom improvement, improved quality of life, and signs of blood loss. Correlation between improved quality of life and blood loss is difficult due to interpatient variability in the assessment of and blood loss and quality of life.

In endometrial carcinoma, total hysterectomy with bilateral oophorectomy is the recommended standard of care. Surgery is also recommended in women with endometrial hyperplasia with atypia, persistent hyperplasia or hyperplasia refractory to medical treatment.[38,39] However, progestins may be considered as a

fertility-sparing option in women hoping to conceive or those who wish to preserve their fertility.[38] Progestins are also utilized as adjuvant therapy in recurrent or metastatic disease, in endothelial hyperplasia without atypia, and in women who are poor surgical candidates.[38] For use of progestins as fertility-sparing therapy, women must have well-differentiated endometrial cancer, absence of suspicious or metastatic disease, disease limited to the endometrium, no contraindications to medical therapy or pregnancy.[38] Guidelines also recommend counseling that fertility-sparing therapy is not the standard of care.[38]

This review evaluates the comparative efficacy of estrogens, progestins, and ospemifene for the treatment of menopause symptoms. Comparative evidence of progestin products for other FDA-approved indications except for contraception is also reviewed.

Table 1. FDA Indications and Dosing of Progestin Products.[21,40]

Drug Name	Indication(s)	Strength/Route	Dose and Frequency
Medroxyprogesterone acetate	• Abnormal uterine bleeding unrelated to menstrual cycle (tablets) • Contraception (SC/IM injection) • Recurrent/metastatic endometrial carcinoma (IM injection) • Prophylaxis of estrogen-induced endometrial hyperplasia (tablets) • Pain associated with endometriosis (SC injection) • Secondary physiologic amenorrhea (tablets)	• 2.5, 5, 10 mg oral tablet • 150, 400 mg/mL IM suspension • 104/0.65 mg/mL SC suspension	• 5-10 mg PO once daily • 150 mg IM or 104 mg SC every 3 months for contraception • 400-1000 mg IM per week for cancer • 104 mg SC every 3 months for endometriosis
Hydroxyprogesterone caproate	• Prevention of preterm birth (brand name Makena® only) • Stage III or IV adenocarcinoma of uterus (generic) • Amenorrhea (generic) • Endometrial disorder (generic)	• 250 mg/mL IM solution	• 250 mg once weekly beginning as early as 16-20 weeks and continuing until 37 weeks or delivery for preterm birth • 1-7 grams weekly for adenocarcinoma • 375 mg once or 250 mg every 4 weeks as cyclic therapy for amenorrhea or endometrial disorders
Norethindrone acetate	• Secondary amenorrhea • Dysfunctional uterine bleeding • Endometriosis	• 5 mg oral tablet	• 2.5-10 mg once daily for amenorrhea or uterine bleeding • 5-15 mg daily for endometriosis
Progesterone	• Abnormal uterine bleeding unrelated to menstrual cycle (injection) • Adjunct therapy to assisted reproductive technology for female infertility (gel, inserts) • Endometrial hyperplasia prophylaxis (capsule) • Secondary physiologic amenorrhea (capsule, injection, gel)	• 50 mg/mL IM oil • 4%, 8% vaginal gel • 100 mg vaginal tablet • 100 mg, 200 mg oral capsule	• 5-10 mg IM once daily x6-8 days for uterine bleeding or amenorrhea • 100 mg vaginal insert BID or TID; 90 mg (8%) daily to BID for infertility • 200 mg PO at bedtime for hyperplasia • 45-90 mg (4-8% gel) every other day; 400 mg PO at bedtime for amenorrhea

Abbreviations: BID = twice daily; IM = intermuscular; IUD = intrauterine device; PO = orally; SC = subcutaneous; TID = three times daily

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, 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. Search for high quality and relevant systematic reviews was limited to the time frame of 2010 to the present. 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:
Menopause
A systematic review and meta-analysis published by the Agency for Healthcare Research and Quality (AHRQ) in 2015 examined the comparative effectiveness, long-term benefits, and long-term adverse effects of medical treatment for menopause symptoms.[1] Symptom relief with commercially prepared estrogen formulations was examined from 283 trials. There was insufficient evidence to evaluate safety or efficacy of compounded hormone therapies. Trials reporting symptoms were included if they were at least 12 weeks in duration. Data were not reported in every trial, but age ranged from 43.8 to 63.5 years with an average 4.1 years since menopause.[1] Approximately 75% of women had a uterus.[1] Results were reported separately for vasomotor symptoms, psychological symptoms, sexual function, urogenital atrophy, sleep disturbances, and quality of life. Because trial outcomes were recorded with different scales and metrics, results were reported using standard mean difference (SMD) with lower numbers indicating a lower frequency of events and higher numbers associated with more events.

There is high strength of evidence that estrogen therapy (at any dose) is more effective than placebo or other medications in treatment of vasomotor symptoms (estrogen vs. placebo SMD ranged from -0.64 to -0.50 corresponding to a decrease of 2 to 3 hot flushes per day).[1] No meaningful difference was observed between estrogen dose (moderate strength of evidence) or route of administration (high strength of evidence).[1] There is high strength of evidence that both SSRI/SNRIs (SMD range -0.43 to -0.31) and estrogen products (SMD range -0.36 to -0.26) improve psychological symptoms (including depression, anxiety, and global psychological well-being).[1] There was insufficient evidence to compare different estrogen strengths, products or formulations. The authors note that presence of these symptoms was typically required for inclusion in trials, but women were often excluded if they were taking psychoactive medications, had a very high score on the assessment tool or had suicidal thoughts.[1] As a result, data may only be applicable to women who have more mild symptoms and who are not on concomitant psychotherapeutic medications. There is high strength of evidence that treatment with vaginal estrogens improve pain with sexual intercourse (SMD -0.54, 95% CI -0.73 to -0.34) and that all estrogens improve overall symptoms of sexual function (SMD 0.27, 95% CI 0.19 to 0.35).[1] There is moderate strength of evidence that oral estrogens improve pain during intercourse (SMD -0.22, 95% CI -0.35 to -0.09), and that all estrogens improve sexual interest (SMD 0.18, 95% CI 0.10 to 0.26).[1] Compared to oral estrogens, vaginal estrogens had a larger treatment effect, but results were not statistically significant (moderate strength of evidence).[1] Because trials reported a variety of outcomes with significant heterogeneity between trials, analysis of differences in dose was not completed. There is high strength of evidence that urogenital symptoms improve with ospemifene (SMD -0.75, 95% CI -1.05 to -0.45), vaginal

estrogens (SMD -0.44, 95% CI -0.65 to -0.23) and oral or transdermal estrogens (SMD -0.35, 95% CI -0.44 to -0.26) compared to placebo with a greater magnitude of effect seen with vaginal versus oral estrogens.[1] Strength of evidence for differences in formulations were not evaluated due to heterogeneity between routes of administration. Evaluation of estrogens on sleep demonstrates a modest improvement compared to placebo (SMD 0.32, 95% CI 0.24 to 0.46; high strength of evidence) with similar treatment effects with other agents (including SSRIs or gabapentin).[1] No difference was observed between standard or low/ultralow doses of estrogen with a SMD of -0.08 (95% CI -0.16 to 0.01) (moderate strength of evidence).[1] Though estrogens have not been directly compared with other sleep therapies, one study did examine the effect of eszopiclone in a similar patient population with a resulting effect size approximately 3-times that of estrogen (SMD 1.08, 95% CI 0.53 to 1.62).[1] Quality of life also improves with estrogen therapy compared to placebo (SMD>0.35) with high strength of evidence.[1] No significant differences were observed between dose or route of administration (moderate strength of evidence).[1] Other agents demonstrate less of an effect on quality of life or have lower quality of evidence.[1] Due to significant heterogeneity between trials, a pooled analysis stratifying patients by age, symptom severity, time since menopause, or uterine status could not be completed.

For evaluation of long-term safety and adverse effects, inclusion criteria required a minimum follow-up of 5 years for trials reporting cancers and a minimum follow-up of at least 1 year for trials reporting other long-term adverse effects.[1] Much of the data from this review were obtained from the Woman's Health Initiative which enrolled a large population of patients who were older and had less severe menopausal symptoms. In order to provide a realistic estimate of the adverse effects in a younger population with more severe symptoms, large observational studies with the target population were included in the meta-analysis. Absolute rates of each adverse effect were not calculated; however, gallbladder disease occurred most frequently with thromboembolic events, stroke and breast cancer occurring less frequently.[1] Combination estrogen/progestin treatment demonstrated an association with increased risk for gallbladder disease (moderate strength of evidence), venous thromboembolism (moderate strength of evidence), stroke (moderate strength of evidence), breast cancer (high strength of evidence), coronary heart disease (moderate strength of evidence), and ovarian cancer (low strength of evidence).[1] Estrogen/progestin combinations decrease colorectal cancer (low strength of evidence) and osteoporotic fractures (moderate strength of evidence) but have no effect on endometrial cancer (moderate strength of evidence).[1] Estrogen alone increases risk for gallbladder disease (moderate strength of evidence), venous thromboembolism (high strength of evidence), and stroke (moderate strength of evidence).[1] Estrogen alone may also decrease risk for breast cancer (low strength of evidence) and osteoporotic fractures (moderate strength of evidence) and have no effect on colorectal cancer (moderate strength of evidence) or coronary heart disease (moderate strength of evidence).[1] Overall, similar trends in long-term adverse effects were demonstrated when patients were stratified based on age or time since menopause.[1] One notable exception was an increased risk of breast cancer in women taking estrogen alone within 5 years of menopause.[1] These results should be interpreted with caution as they were exploratory endpoints based on only a few studies. Other systematic reviews have noted similar increased risk of stroke in women currently on therapy (HR 1.32, 95% CI 1.12 to 1.56; p=0.001) which decreased after treatment discontinuation (HR 1.00, 95% CI 0.85 to 1.16; p=0.958).[41]

Another analysis of HRT was published by the National Institute for Health and Care Excellence (NICE) in a 2015 systematic review and guideline update.[4] The review included both RCTs and observational studies and examined the short and long-term risks and benefits of HRT. Because direct comparison between different interventions was not available, a network meta-analysis was used to estimate relative treatment effects. Separate analyses were conducted for individual patient populations (i.e. women with a uterus or women with a history of breast cancer).[4] The analyses were limited by availability of data; a number of studies were excluded due to lack of reported data on outcomes or individual patient populations.[4] Because many studies were excluded, there was considerable uncertainty in the estimates of treatment effects; and guideline recommendations regarding effective treatment were strongly influenced by current practice standards and clinical expertise.[4] In women with a uterus (n=4,165), estrogen/progestin combination patches were the most effective compared to placebo for the treatment of vasomotor symptoms (mean ratio [MR] 0.23, 95% CI 0.09 to 0.57).[4] Indirect comparisons between agents suggested that non-oral estrogens were more effective than raloxifene (MR 7.12, 95% CI 1.86 to 27.63) or SSRI/SNRIs (MR 3.63, 95% CI 1.33, 9.93).[4] Other comparisons failed to

demonstrate statistical differences for the treatment of vasomotor symptoms.[4] In addition, non-oral estrogen/progestin and estrogen/bazedoxifene combinations were overall better tolerated than SSRI/SNRIs with fewer patients discontinuing therapy.[4] Data in women without a uterus were not used to influence guideline recommendations due to lack of relevant included data on hormonal interventions.[4] Guideline recommendations for women without a uterus were based on extrapolated data from the analysis of women with a uterus.[4] Therapies analyzed for the treatment of vaginal symptoms included local estrogens or ospemifene. Evidence supporting the use of local estrogens was low quality, with moderate quality evidence for ospemifene.[4] Evidence was insufficient to evaluate differences in efficacy between estrogen dose.[4]

Long-term effects of HRT were also assessed in the 2015 systematic review by NICE using observational and randomized control data. Estimated magnitude of treatment effects were summarized based on study type (RCT or observational), timing and duration of treatment, and type of therapy (estrogen alone, estrogen/progestin combinations, or any HRT).[4] A summary of results from these analyses is presented here. Overall, oral HRT (with and without progestins) increased risk of VTE compared to placebo.[4] Risk was not significantly different from placebo when comparing transdermal HRT to placebo.[4] An analysis of VTE risk associated with different progestin products was not conducted because individual trials demonstrated significantly heterogeneous outcomes.[4] No correlation was observed between cardiovascular disease or coronary heart disease risk and use of HRT (with and without a progestin) based on low quality evidence.[4] Evidence from some observational studies does suggest an increased risk of stroke associated with HRT, but absolute risk remains low.[4] There was insufficient evidence to evaluate the cardiovascular risk associated with differences in specific preparations, formulations, or dosages.[4] Evidence also demonstrated that risk of MI, cardiovascular disease, or cardiovascular mortality was not increased in women less than 65 years of age treated with estrogen or combined estrogen/progestin formulations.[4] Risk of stroke was increased in women treated with HRT, but absolute risk remained small.[4] Limited evidence suggested that transdermal estrogen may have lower risk of stroke compared to oral preparations.[4] Risk of CHD was not increased with estrogen alone, and there was little to no risk with combination estrogen and progestin treatment.[4] In addition, risk of bone fractures was decreased in women currently taking HRT, but risk returned to baseline once HRT was discontinued.[4] Patients with longer duration of therapy may have larger benefit upon discontinuation.[4] Patients taking combination estrogen/progestin therapy also demonstrated an increased risk of breast cancer, but little to no change was observed in women taking estrogen only therapy.[4] Risk was correlated with treatment duration and returned to normal after treatment discontinuation.[4] No correlation was observed between HRT use and development of type 2 diabetes or adverse effects on blood glucose control (low quality of evidence).[4]

A systematic review specifically examined risk of endometrial cancer from HRT in patients with a prior history of surgical treatment for endometrial cancer.[6] The review included 1 RCT and 5 observational studies (n=1,975).[6] Overall, use of HRT did not increase risk of cancer recurrence in patients with prior surgical treatment of endometrial cancer. Results demonstrate that risk of endometrial cancer was, in fact, decreased in patients who received HRT (OR 0.53, 95% CI 0.30 to 0.96).[6] However, there was moderate heterogeneity between studies (I^2=49%).[6] In addition, estrogen dose and baseline risk factors for recurrence varied between study groups.[6] Due to limitations in reporting and observational study design, authors recommend interpretation of these results with caution.[6] Results cannot exclude the potential for increased risk of endometrial cancer in women with prior history, but overall results demonstrate that magnitude of this risk is likely small.[6] Similarly, in a review of patients with a prior history of surgical treatment for epithelial ovarian cancer, HRT use was not associated with decreased survival (HR 0.69, 95% CI 0.61 to 0.79).[7] Two RCTs and 4 cohort studies (n=1448 [n=419 with HRT]) were included in this analysis.[7] Authors note that due to the limitations in population and study design of included trials, further well-designed trials are necessary to verify these results.[7]

A Cochrane systematic review updated in 2015 examined the risks and benefits of oral HRT (with or without a progestin) for use in the primary or secondary prevention of cardiovascular disease in postmenopausal women.[42] The review included 19 randomized controlled trials which enrolled over 40,000 women at an average age of 64 years.[42] Interventions included 17β-estradiol, estradiol valerate, and conjugated equine estrogen alone or in combination with medroxyprogesterone acetate or norethindrone.[42] Mean follow-up in the majority of patients was more than 5 years, and 7 trials were discontinued early as

benefits of therapy were unlikely to outweigh cardiovascular risks. With use in primary prevention, there was no difference in all-cause mortality (RR 1.00, 95% CI 0.89 to 1.12) or any cardiovascular disease outcomes.[42] Risk of stroke (RR 1.32, 95% CI 1.12 to 1.56), venous thromboembolism (RR 1.92, 95% CI 1.24 to 2.99), and pulmonary embolism (RR 1.89, 95% CI 1.17 to 3.04) were significantly increased in women taking HRT compared to placebo.[42] Similarly, when used as secondary prevention, an increased risk of venous thromboembolism was observed (RR 2.02, 95% CI 1.13 to 3.62) but no difference was seen in other cardiovascular or mortality outcomes.[42] However, patient population utilizing HRT as secondary prevention were significantly smaller compared to primary prevention trials and may not have been sufficient to detect differences in these outcomes. Exploratory analyses were conducted examining how duration and timing of treatment affected outcomes. Caution should be taken when interpreting the results of these analyses as there was significant heterogeneity between hormone therapy regimens and patient populations in different trials.[42] Differences in outcomes at different times may be due to differences in population studied. Overall, there was no difference in mortality for patients taking hormone therapy for one to 8 years.[42] However, based on the results from 2 studies, patients treated for 10 years with HRT had a higher survival rate than those given placebo (RR 0.55, 95% CI 0.31 to 0.96).[42] Subgroup analysis for timing of HRT (less than or greater than 10 years) after menopause were also completed. If information on time since menopause was not available, mean age of participants greater or less than 60 years was used as a surrogate.[42] Compared to placebo, all-cause death (RR 0.70, 95% CI 0.52 to 0.95; p=0.01) and coronary heart disease (a composite of death from cardiovascular disease and non-fatal myocardial infarction [MI]; RR 0.52, 95% CI 0.29 to 0.96; p=0.02) and venous thromboembolism (RR 1.74, 95% CI 1.11 to 2.73) were significantly higher in women starting HRT within 10 years of menopause (n=9,629).[42] In women starting HRT more than 10 years after menopause (n=28,705), no difference was seen in mortality (RR 1.06, 95% CI 0.95 to 1.18) or coronary heart disease (RR 1.07, 95% CI 0.96 to 1.20) compared to placebo.[42] However, these women did have a higher risk of stroke (RR 1.21, 95% CI 1.06 to 1.38) and venous thromboembolism (RR 1.96, 95% CI 1.37 to 2.80).[42] Overall thromboembolic events were observed more frequently in patients taking combination estrogen and progestin therapy.[42] Incidence of stroke was mainly driven by ischemic rather than hemorrhagic events.[42]

Other systematic reviews examining efficacy of low dose transdermal estrogens (defined as less than 0.05 mg of 17β-estradiol or equivalent) [43] and bioidentical hormone products [44] have demonstrated similar improvements for the treatment of vasomotor symptoms. Bioidentical hormone products are typically compounded preparations and contain hormones with an identical chemical structure to hormones produced by the ovaries. Low dose transdermal estrogens decreased the number of daily hot flashes by an average of 7.07 to 9.36 depending on the estrogen dose compared to an average decrease of 5.07 in the placebo groups.[43] Frequency of hot flushes with use of bioidentical hormone products was also reduced in 793 women using a patch, 356 women on oral formulations, and 458 women on intranasal formulations with treatment effects of SMD -0.68 (95% CI -0.83 to -0.53), SMD -0.80 (95% CI -1.03 to -0.57), and SMD -3.04 (95% CI -4.05 to -2.03) respectively.[44] In comparison to conjugated estrogens, bioidentical hormone patches or oral formulations did not demonstrate any significant difference in frequency of hot flushes, though the authors note that the quality of evidence was too low to reach a definitive conclusion.[44] Reports of adverse effects compared to conjugated estrogens were inconsistent with one trial reporting more frequent breast pain and vaginal bleeding in the bioidentical hormone group and others reporting no difference in adverse effects.[44]

A systematic review conducted in 2014 specifically examined the efficacy of vaginal estrogens for the treatment of genitourinary symptoms of menopause including vaginal dryness, burning, dyspareunia, dysuria, urgency or frequency.[45] The review included 44 studies in postmenopausal women with genitourinary symptoms of menopause.[45] Trials compared vaginal estrogen to placebo, other types of vaginal estrogen, formulations designed to deliver a systemic dose of estrogen (i.e. vaginal ring, transdermal patch, or oral administration), and non-hormonal moisturizers or lubricants.[45] A meta-analysis was not completed, but evidence was graded based on scientific merit, likelihood of bias and completeness of reporting. Overall, estrogen formulations improved complaints of dryness, itching, burning and dyspareunia (moderate quality evidence), urinary complaints including dysuria and urinary urgency (low to very low quality evidence), stress urinary incontinence (low quality evidence), and urgency urinary incontinence (moderate quality evidence).[45] No difference was observed in symptom improvement between vaginal estrogen and systemic formulations (low to very-low quality evidence).[45]

A systematic review performed in 2014 by CADTH examined risks and benefits of oral progesterone for the treatment of menopausal symptoms.[46] The review included 6 studies from the Women's Health Initiative (WHI), data from the Million Women prospective cohort study, and 2 RCTs from Canada and Finland. The mean age of women in the WHI (63.2 years) was significantly older than women in other included studies (mean range 52.5 to 56.7 years).[46] The review found that compared to placebo, combined conjugated equine estrogen and medroxyprogesterone increase risk of breast cancer (2.6 vs. 1.3 per 10,000 women per year), death due to breast cancer (5.3 vs. 3.4 per 10,000 women per year), and deaths due to lung cancer (HR 1.71, 95% CI 1.16 to 2.52, p=0.01) largely based on data from the WHI.[46] However, as lung cancer was not a pre-specified outcome in the WHI, these results should be interpreted with caution. Increased risk of atrial fibrillation was not associated with medroxyprogesterone use. In the Million Women Study, women taking estrogen with medroxyprogesterone also had increased risk of VTE (RR 2.67, 95% CI 2.25 to 3.17) compared to women who had never used HRT.[46] Rates of VTE were also significantly higher with medroxyprogesterone use than norethindrone or norgestrel.[46] Only one small study examined the efficacy of oral progestins in the treatment of vasomotor symptoms. The study, conducted in early postmenopausal women, found decreased vasomotor symptoms with oral progestins which were not statistically significant compared to placebo.[46] The study was limited by small sample size, short treatment duration, and unblinding of treatments during the study. There were no other studies directly examining comparative efficacy or safety of different oral progestins.

Another systematic review examined association of low dose HRT (with or without progestins) with metabolic control in postmenopausal women with diabetes mellitus.[5] Previous epidemiologic studies and trials have noted the relationship between HRT and improved diabetes risk, but this is the first systematic review which summarizes this data.[5] The review included 8 studies (n=16,807) which evaluated the risk of diabetes in women on HRT and 8 studies (n=1,164) evaluating the effect of HRT on glycemic control in current diabetics via fasting blood glucose, glycated hemoglobin (HbA1c), and lipid profiles.[5] Results indicate that patients who had used HRT had a significantly lower rate of diabetes compared to patients who had never used HRT (OR 0.61, 95% CI 0.55 to 0.68).[5] In patients who were currently diabetic, diabetic indices including HbA1c (mean difference [MD] -0.73%, 95% CI -1.28 to -0.18%) and LDL (MD -0.43 mM/L, 95% CI -0.71 to -0.14 mM/L) demonstrated statistically significant improvement compared to placebo, though results may not be clinically significant.[5]

Uterine Bleeding

A Cochrane systematic review conducted in 2015 examined the safety and efficacy of progestin products (including oral and IUD) for reduction of heavy menstrual bleeding.[11] They included 21 studies, 7 of which examined efficacy of oral medications compared to an IUD.[11] Effectiveness was measured using either PBAC sores or the alkaline haematin method.[11] There was no statistically significant difference in efficacy between a levonorgestrel IUD and 15-25-day oral progestins or 10-day medroxyprogesterone acetate, but combined oral contraceptives had significantly less reduction of heavy menstrual bleeding compared to an IUD (alkaline haematin: MD 66.91 mL, 95% CI 42.1 to 91.20 mL; PBAC: MD 55.05 mL, 95% CI 27.83 to 82.28 mL).[11] Studies had significant heterogeneity, but the direction of treatment effect consistently favored use of an IUD compared to oral progestins.[11] Adverse effects and serious adverse events were mostly similar between groups with an increase in pelvic pain (RR 2.68, 95% CI 1.00 to 7.18), breast tenderness (RR 2.85, 95% CI 1.29 to 6.29) and ovarian cysts (RR 3.28, 95% CI 1.31 to 8.21) in women with a levonorgestrel IUD.[11] Other systematic reviews demonstrated similar trends[12,13] with greatest reduction in menstrual blood loss with levonorgestrel IUD (71% to 95%) compared to combined oral contraceptives (35 to 69%) or oral progestins (20 to 67%).[12]

Endometrial carcinoma and hyperplasia

A systematic review of 34 observational studies (n=559) published in 2012 examined regression, relapse and live birth rates in women using progestins for treatment of atypical complex endometrial hyperplasia and endometrial carcinoma.[14] Women included in these studies generally had well-differentiated endometrial carcinoma.[14] Half-of the studies included in this review were prospective cohort studies, none were blinded to treatment assignment, and only six had an adequate follow-up of 5 years.[14] Case reports or case series were excluded if they reported fewer than 5 cases.[14] Follow-up ranged from 11 to 72

months.[14] In women diagnosed with endometrial carcinoma, rates of cancer regression and live births were 76.2% (95% CI 68 to 85.3%) and 28.0% (95% CI 21.6 to 36.3%), respectively.[14] Similar rates were observed in women with endometrial hyperplasia.[14] However, relapse rates after initial regression were also high in women with endometrial carcinoma (40.6%, 95% CI 33.1 to 49.8%) and endometrial hyperplasia (26%, 95% CI 18.5 to 37.4%).[14] In addition, 20 women (3.6%) developed ovarian malignancies during follow-up.[14] The authors concluded that fertility-sparing treatment with progestins may be an option for women with endometrial cancer who would like to conceive.[14] However, because of high relapse rates, the authors continue to recommend typical treatment of surgery as soon as possible after conception.[14] Similar results were noted in another systematic review examining the efficacy of oral progestins for treatment of endometrial carcinoma or hyperplasia over a mean follow-up time of 45.8 months.[15] Rates of complete pathological response to progestins were 74% (95% CI 65 to 81%) in women with endometrial carcinoma and 72% (95% CI 62 to 80%) in women with endometrial hyperplasia.[15] Live births occurred in 34 (34.0%) of patients trying to conceive, and relapse upon long term follow-up occurred in 32 patients (20.1%).[15]

Another systematic review examined the efficacy of levonorgestrel IUD compared to oral progestin therapy in women with endometrial hyperplasia without atypia.[47] Seven RCTs (n=766) conducted in Turkey, Egypt, Kuwait and Iran were included in the analysis.[47] Patients in these trials were randomized to oral medroxyprogesterone acetate or norethindrone acetate versus levonorgestrel IUD. Therapeutic response was significantly improved in patients receiving an IUD compared to patients receiving oral therapy at all time points measured from 3 months (OR, 2.30, 95% CI 1.39 to 3.82; P=0.001, 5 trials, n=376) to 24 months (OR, 7.46; 95% CI 2.55 to 21.78; P=0.0002, 1 trial, n=104).[47] Therapeutic response was defined slightly differently in various trials but typically consisted of proliferative or atrophic pattern endometrium upon biopsy.[47] Rates of irregular vaginal bleeding were significantly more common in patients with an IUD than oral therapy (OR 1.92, 95% CI 1.14 to 3.23, 3 trials, p=0.01).[47]

Endometriosis

A Cochrane systematic review examined the efficacy of various interventions in the improvement of pain and fertility outcomes in women with endometriosis. This review compiled results from multiple Cochrane systematic reviews to evaluate best treatment options for endometriosis. Oral progestins examined in this review included combination estrogen and progestins or progestins alone versus placebo. Results demonstrated no consistent difference in pain or fertility outcomes compared to placebo though evidence was of low quality.[8] The authors concluded that evidence for oral progestins has not demonstrated significant benefits in pain relief or improved fertility outcomes.[8]

Another systematic review conducted in 2011 examined efficacy of various treatments including progestins, combined oral contraceptives, and gonadotropin releasing hormone agonists.[33] The analysis included a total of 7 RCTs (n=1096), 5 of which included progestin therapy, and defined an improvement in pain as at least a 1 point improvement in pain score at the end of treatment.[33] Mean duration of treatment was 7 months (range 3 to 12 months).[33] Overall, for the treatment of pain progestins (either IUD, depot-medroxyprogesterone acetate, or combined oral contraceptives) demonstrated no significant difference from gonadotropin releasing hormone agonists (RD 0.036, 95% CI 0.03 to 0.102).[33] Upon comparison of IUD versus depot-medroxyprogesterone acetate, no difference in endometriosis associated pain was observed (RD -0.006, 95% CI -0.124 to 0.162).[33] Data from 1 trial demonstrated that progestins were also less effective than combined oral contraceptives for the treatment of pain with endometriosis (RD 0.321, 95% CI -0.066 to 0.707).[33] These results were limited by the small sample size and quality of included studies.

Prevention of preterm birth

A Cochrane systematic review in 2013 examined 36 randomized control trials (8523 women and 12,515 infants) utilizing progesterone (intramuscular, oral or vaginal) for the prevention of preterm birth.[16] Women included in the study had a history of spontaneous preterm birth, short cervix identified on ultrasound, or a multiple pregnancy. Results demonstrated that women with a history of spontaneous preterm birth had a significant reduction of perinatal mortality (RR 0.50,

95% CI 0.33 to 0.75), preterm birth at 34 weeks (RR 0.31, 95% CI 0.14 to 0.69), and preterm birth at 37 weeks (RR 0.55, 95% CI 0.42 to 0.74) with progesterone use compared to placebo.[16] Secondary outcomes of infant birthweight, assisted ventilation, necrotizing enterocolitis, and admission to neonatal ICU were also statistically lower in women taking progesterone.[16] In women with a short cervix, progesterone use was associated with similar decreased risk of preterm birth at 34 weeks (RR 0.64, 95% CI 0.45 to 0.90), but had no difference in perinatal mortality or other secondary outcomes compared to placebo.[16] No difference in efficacy was observed between doses or routes of administration.[16] In addition, in women with a multiple pregnancy or women with threatened preterm labor, there was no difference in any outcome including perinatal death or preterm birth as 34 weeks.[16] Other systematic reviews have demonstrated similar trends for women with a history of preterm birth in reduction of clinical neonatal outcomes with the use of vaginal[17-19] and systemic progestins.[19,48]

A review conducted by NICE in 2015 examined 13 studies to determine the efficacy of oral or vaginal progesterone for prevention of preterm birth in high-risk women.[49] High-risk women were defined as women with a previous history of spontaneous preterm birth or a short cervix.[49] The intramuscular formulation of hydroxyprogesterone caproate was not evaluated in this study. Significant heterogeneity existed between trials with differences in assessment of cervical length, inclusion criteria, dosing, timing and duration of progesterone use. However, direction of effect was consistent, demonstrating benefit with progesterone use. In women with a history of spontaneous preterm birth, significantly lower risk of preterm birth was demonstrated with vaginal progesterone at 37 weeks (moderate quality evidence) and oral progesterone at 34 weeks (moderate to high quality evidence).[49] However, results for other outcomes (including preterm birth at other times, perinatal mortality, neonatal death, and neonatal sepsis) failed to reach statistical significance.[49] In women with ultrasound identified short cervix, vaginal progesterone significantly decreased preterm births at 28, 33 and 35 weeks compared to placebo.[49] No difference was observed in other outcomes of perinatal mortality, intrauterine fetal death, neonatal death, preterm birth at 37 weeks, bronchopulmonary dysplasia or neonatal sepsis (moderate to low quality evidence).[49] In addition in one small RCT, no difference was observed between perinatal death, neonatal morbidity or preterm birth upon comparison of prophylactic cerclage and prophylactic progesterone (low quality evidence).[49]

A review from CADTH was published in 2014 specifically examining the efficacy of vaginal micronized progesterone capsules for the prevention of miscarriage and preterm birth. The review was primarily based on 3 studies which included 1027 women.[50] Because of variability in population between the studies, a meta-analysis was not conducted. Overall, results from the studies suggest that progesterone capsules compared to placebo may decrease risk of preterm birth at less than 37 or 34 weeks.[50] However, statistical significance in individual studies varied, and the authors recommend careful interpretation of these results.[50] For example, relative risk for preterm birth at 37 weeks reached statistical significance in only 1 trial (RR 0.32, 95% CI 0.14 to 0.72).[50] For prevention of preterm birth at 34 weeks, all 3 trials demonstrated similar trends, but only 1 trial achieved statistical significance (RR 0.58, 95% CI 0.35 to 0.87).[50] Results also varied for the 2 trials reporting improvement with birth weight less than 2,500 g (RR 0.96, 95% CI 0.73 to 1.27) and (RR 0.88, 95% CI 0.79 to 0.98) and admission to the neonatal intensive care unit (RR 0.11, 95% CI 0.01 to 2.01) and (RR 0.89, 95% CI 0.79 to 0.99).[50] All other maternal or neonatal outcomes failed to reach statistical significance.[50]

Another systematic review in 2015 examined effectiveness of progestins in women with twin pregnancies based on a review of individual patient level data.[51] The review included 13 RCTs (n=3,768 women, 7,536 babies) that compared vaginal progesterone or intramuscular hydroxyprogesterone caproate to placebo or no treatment.[51] Women were on average 32 years of age, Caucasian (78-90%), and had a mean gestational age of 19-20 weeks at randomization.[51] The primary outcome was a composite of adverse perinatal outcomes defined based on the availability of data in the trials.[51] It included perinatal death (fetal death or death before hospital discharge) or significant neonatal morbidity.[51] Significant morbidity was a composite of respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular hemorrhage, necrotizing enterocolitis, and culture-proven sepsis for the hydroxyprogesterone caproate group, but only included respiratory distress syndrome, intraventricular hemorrhage, and necrotizing enterocolitis for the vaginal progesterone group.[51] Overall, there was no difference in adverse perinatal outcomes for women given hydroxyprogesterone caproate versus placebo (RR 1.2, 95% CI 0.87 to 1.5) or vaginal progesterone (RR 0.96, 95%

CI 0.83 to 1.1).[51] Individual components of the composite were also similar between groups.[51] A pre-specified subgroup analysis of adverse perinatal outcomes in women with a cervical length of less than 25 mm was significantly improved in women receiving vaginal progesterone compared to placebo (RR 0.57, 95% CI 0.47 to 0.70; NNT 10).[51] Outcomes were not improved in a similar population (women with a cervical length <25 mm) receiving hydroxyprogesterone caproate or in other populations receiving vaginal progesterone.[51] In a prior systematic review published in 2013, use of vaginal estrogen had demonstrated improved neonatal morbidity and mortality in women with twin gestation, short cervix, and no previous preterm birth (RR 0.52, 95% CI 0.29 to 0.93).[18] This review was limited by the small number of included studies (n=5) and a limited patient population (n=775 women, 827 infants).[18]

A recently published systematic review examined evidence comparing intramuscular hydroxyprogesterone caproate and vaginal progesterone for prevention of recurrent preterm birth in women with a singleton pregnancy.[20] The review included 3 randomized control trials directly comparing vaginal progesterone formulations to 250 mg intramuscular hydroxyprogesterone (n=680).[20] Formulations of vaginal progesterone included 90 mg vaginal gel daily and 100 and 200 mg suppositories daily.[20] Women in these trials had a history of prior preterm birth and were on average 16 weeks pregnant at the time of randomization. Overall, women treated with vaginal progesterone had a significantly lower rate of preterm birth at 34 weeks (17.5% vs 25.0%; RR 0.71, 95% CI 0.53 to 0.95) and 32 weeks (8.9% vs 14.5%; RR 0.62, 95% CI 0.40 to 0.94) compared to intramuscular hydroxyprogesterone, but no difference at 37, 28 or 24 weeks.[20] In addition, vaginal progesterone was associated with a lower rate of admission to the neonatal intensive care unit (18.7% vs 23.5%; RR 0.63, 95% CI 0.47 to 0.83).[20] No difference was observed in other clinically important neonatal outcomes.[20] Adverse drug reactions were also reported more frequently in women randomized to intramuscular hydroxyprogesterone compared to vaginal progesterone (7.1% vs 13.2%; RR 0.53, 95% CI 0.31 to 0.91).[20] The specific nature of these adverse effects was not reported, but common adverse effects associated with hydroxyprogesterone caproate include injection site reactions. All outcomes were graded as low quality of evidence due to the small population size, large variance associated with the estimated treatment effect, and differences in vaginal formulations.[20]

Clinical Practice Guidelines:

Menopause Symptoms

The Endocrine Society developed new clinical practice guidelines in 2015 assessing management and treatment of symptoms of menopause.[24] HRT can be considered for treatment of vasomotor symptoms in women less than 60 years of age or less than 10 years past menopause who do not have contraindications to therapy including high cardiovascular or breast cancer risk (weak recommendation with low quality evidence).[24] Authors note that there is no consensus opinion among professional societies regarding relative and absolute contraindications, but they generally recommend avoiding HRT in women with unexplained vaginal bleeding, active liver disease, and history of breast cancer, endometrial cancer, or cardiovascular disease (stroke, transient ischemic attack, pulmonary embolism, VTE, and MI).[24] Caution is advised in patients with diabetes, hypertriglyceridemia greater than 400 mg/dL, active gallbladder disease, increased risk of cardiovascular disease or breast cancer, and migraine with aura.[24] Estrogen alone can be utilized in women without a uterus, but estrogen plus progestin therapy is recommended in women with a uterus due to increased risk of endometrial hyperplasia and cancer with estrogen alone (weak recommendation with low quality evidence).[24] Combination conjugated equine estrogens with bazedoxifene may also be utilized in postmenopausal women with a uterus to relieve vasomotor symptoms and prevent bone loss (weak recommendation based on moderate quality evidence).[24] Non-hormonal agents are recommended as first-line therapy in women with high risk of cardiovascular disease or high (5-year risk >5%) to intermediate (5-year risk >1.67%) risk of breast cancer (weak recommendation with low quality evidence).[24] High-risk cardiovascular conditions include prior MI, cerebrovascular disease, peripheral arterial disease, abdominal aortic aneurism, diabetes, chronic kidney disease or a 10-year cardiovascular disease risk greater than 10%. Women with moderate (unspecified) cardiovascular risk may consider transdermal estradiol and progestins without an adverse metabolic profile (weak recommendation with low quality evidence).[24] In women a prior history of VTE, preferred therapy includes low-dose, non-oral estrogens (strong recommendation with low quality evidence) and a progestin such as progesterone with fewer adverse coagulation parameters (strong recommendation with moderate quality evidence).[24] Preferred treatment for

moderate to severe genitourinary symptoms is low-doses vaginal estrogen after a failed trial of vaginal moisturizers or lubricants (strong recommendation with moderate quality evidence).[24] In women with a uterus utilizing low dose vaginal estrogen, concurrent progestin therapy for prevention of endometrial hyperplasia is not required (weak recommendation with very low quality evidence).[24] Ospemifene may be considered in women with moderate to severe dyspareunia (weak recommendation with moderate quality evidence), but is not recommended in women with a history of breast cancer (strong recommendation with very low quality evidence).[24] In patients with a history of estrogen dependent cancer, prescription vaginal estrogen should be considered only in consultation with an oncologist.[24]

Guidelines from NICE for the evaluation and treatment of menopause were updated in 2015 based on a recent systematic review.[4] The review included both RCTs and observational studies and evaluated quality of evidence for both short and long-term risks and benefits of HRT. Strength of recommendations was not assessed. Because many studies were excluded from the analysis, there was considerable uncertainty in the estimates of treatment effects; and guideline recommendations were strongly influenced by current practice standards and clinical expertise.[4] Guidelines suggest utilization of estrogen plus progesterone (oral or transdermal) in women with a uterus, and estrogen alone in women without a uterus as first-line treatment of vasomotor symptoms.[4] HRT are also the preferred pharmacological options for mood symptoms as a result of menopause, though cognitive behavioral therapy may also be used as initial treatment.[4] SSRIs/SNRIs are not recommended as a first-line option due to their significant adverse effect profile and their lack of data in women who have not been diagnosed with depression.[4] Vaginal HRT was recommended as the preferred first-line treatment for vaginal symptoms, and it may be used in combination with systemic HRT formulations.[4] Due to limitations in economic data, no recommendations were made regarding ospemifene for the treatment of vaginal symptoms. Treatment should be individualized based on patient specific risk factors for adverse effects including breast cancer, endometrial cancer, and VTE.[4] Other long-term factors that may influence treatment choice include a patient's individual risk for MI, stroke, fragility fractures, or dementia. Transdermal estrogens are recommended in patients with increased or high risk of VTE as they have demonstrated a lower risk compared to oral therapy.[4] Referral to a hematological specialist may be beneficial to assess appropriate therapy in patients with high risk of VTE.[4] There was insufficient evidence to recommend HRT over combined oral contraception in women with primary ovarian insufficiency (POI) .[4] In POI, treatment with either HRT or combined oral contraceptives are recommended until the age of natural menopause (unless contraindicated).[4] Evidence to support recommendations for the optimum time to assess efficacy and safety of HRT was also lacking.[4] Current practice includes assessment after 3 months to determine effectiveness and tolerability and at least annually thereafter.[4] Upon comparison of abrupt discontinuation compared to tapering methods, no strong difference was found in short- or long-term symptom relief.[4] Guidelines recommend discontinuation methods be individualized based on patient preferences.[4]

Uterine Bleeding

NICE guidelines, published in 2007 and updated in 2016, recommend use of either hormonal or non-hormonal therapy in cases of heavy menstrual bleeding without presence of fibroids or with fibroids less than 3 cm in diameter (based on non-comparative studies or expert opinion).[52] Options are considered in the following order, but should take individual circumstances into account: 1) levonorgestrel IUD if at least 12 months of use is anticipated (based on high quality evidence from at least 1 systematic review or RCT), 2) non-hormonal options or combined oral contraceptives (based on high quality systematic reviews of observational studies with consistent direction of effect), and 3) norethindrone 15 mg daily from days 5 to 26 or injected long-acting progestins (based on high-quality evidence from at least 1 systematic review or RCT).[52] Guidelines recommend against the use of oral progestins given for only 12 to 14 days each month due to decreased efficacy (based on high quality evidence from at least 1 systematic review or RCT).[52]

Guidelines from the Society of Obstetrics and Gynaecology of Canada (SOGC) recommend use of hormonal therapy to reduce heavy menstrual bleeding in women who desire effective contraception after malignancy or significant pelvic pathology has been ruled out.[34] Recommended regimens include combined oral contraceptives, depot-medroxyprogesterone acetate or levonorgestrel IUD.[34] Use of long phase progestins (from days 5 to 26) may also be considered though

they may be associated with more adverse effects.[34] However, use of cyclic oral progestins taken for 12 to 14 days each month is not recommended as a specific treatment for heavy menstrual bleeding because these regimens are less effective at reducing blood loss.[34] Recommendations were based on good evidence from at least one RCT.[34] Recommendations from the American College of Obstetricians and Gynecologists include similar treatment options of combined oral contraceptives, oral progestins, and the levonorgestrel-releasing IUD (based on limited or inconsistent scientific evidence).[53] Choice of medical treatment is individualized based on the goals of treatment (i.e. to stop acute bleeding, avoid future irregular bleeding, provide contraception, or prevent future complications of anemia, surgery and decreased quality of life) (based on limited data and expert opinion).[53]

Endometrial carcinoma and endometrial hyperplasia

National Comprehensive Cancer Network guidelines for the treatment of uterine neoplasms have strict recommendations for the use of fertility-sparing options for treatment of endometrial carcinoma.[38] All recommendations regarding use of progestins as fertility-sparing therapy for endometrial carcinoma are based on low level evidence with uniform consensus from panel members.[38] Typical standard of care for endometrial cancer includes either surgery or radiation. Hormone therapy may be considered in patients who are not candidates for surgery or radiation or in women desiring fertility-sparing treatment options.[38] Because use of progestins is not the typical standard of care in endometrial cancer, women considering progestin use must have a well-differentiated endometrioid adenocarcinoma limited to the endometrium with absence of suspicious or metastatic disease.[38] Recommended progestins include megestrol acetate, medroxyprogesterone or a levonorgestrel IUD.[38] Treatment option should be individualized based on patient specific risk factors and contraindications with follow-up every 3 to 6 month to assess disease response. In women with early stage endometrial cancer, data suggest that though the recurrence rate is high (35%) in women taking progestins, therapy has not been associated with an increased risk of cancer-related mortality.[38] For women trying to conceive, consultation with a fertility expert prior to therapy is recommended.[38] Surgery with total hysterectomy is recommended if patients have a documented progression, continued disease, or have completed childbearing.[38] Hormone therapy (including the use of progestational agents, aromatase inhibitors or selective estrogen receptor modulators) also has a role as systemic therapy for recurrent, metastatic or high-risk disease in patients with low grade endometrial histology, small tumor volume, or carcinoma with an indolent growth rate.[38]

Endometriosis

Guidelines published in 2010 from Society of Obstetrics and Gynaecology of Canada for the treatment of endometriosis recommend continuous combined oral contraceptives or progestin therapy alone (oral, injected, or IUD) as first-line therapy (Grade 1A: good evidence to recommend action from at least 1 RCT).[10] The guideline authors note that though these medications are commonly used in practice, little evidence compares their efficacy with other medications.[10] Indeed, more recently published systematic reviews (discussed in detail above) note that progestins have limited utility for improvement of pain-related outcomes in endometriosis.[8,33] Agents specifically mentioned in these guidelines include norethindrone acetate 5 to 20 mg daily, intramuscular or subcutaneous medroxyprogesterone acetate, and the levonorgestrel-releasing IUD.[10] Choice of therapy depends on adverse effects. Norethindrone acetate and medroxyprogesterone acetate can have heavy breakthrough bleeding. In addition, injection therapy is not the best option for women trying to conceive as it can result in prolonged delay in resumption of ovulation.[10] The interuterine system is another long-term treatment which is inserted for 5 years and delivers levonorgestrel directly to the site of action. It can be effective at managing pain but is associated with an increased risk of pelvic infections.[10] Regarding infertility associated with endometriosis, no medications have been identified which improve fertility outcomes and medication management should not be offered (Grade 1E: good evidence to recommend against action from at least 1 RCT).[10]

Similar treatment options are recommended for endometrial associated pain by the American College of Obstetricians and Gynecologists in a practice bulletin published in 2010 and reaffirmed in 2014.[9] Medical suppressive therapy may be used to improve pain associated with endometriosis but has no effect on fertility outcomes (recommendation based on good and consistent evidence).[9] Hormonal treatment options include combined oral contraceptives or progestin therapy

alone. The guidelines make recommendations for oral contraceptives, oral norethindrone or depot-medroxyprogesterone acetate in women with known endometriosis and dysmenorrhea (based on limited or inconsistent evidence).[9] They also note that long-term use of oral contraceptives (>24 months) has been shown to reduce endometrioma recurrence and symptoms of dysmenorrhea (based on limited or inconsistent evidence).[9]

Prevention of preterm birth

NICE guidelines for prevention of preterm labor suggest offering prophylactic progesterone to women with a cervical length of less than 25 mm (with or without previous history of preterm birth or pregnancy loss).[49] Progesterone may also be considered in women with a cervical length less than 25 mm who have had pre-term pre-labor rupture of membranes in a previous pregnancy or women with a history of cervical trauma.[49] Both progesterone and cervical cerclage have demonstrated benefit in women with a history of preterm birth, but there is limited evidence regarding their comparative efficacy and safety.[49] NICE guidelines recommend against the use of intramuscular or vaginal progesterone to prevent spontaneous preterm birth in twin or triplet pregnancies.[54] Strength of these recommendations was not rated. The guideline committee concluded that evidence for benefit of therapy was not high enough to recommend for all women at risk of preterm birth, and evidence for risks of therapy was not high enough to recommend against its use in this population.[49]

New Safety Alerts:

Since 2014, contraindications for Estrasorb® (estradiol topical emulsion), Evamist® (estradiol transdermal spray), and Cenestin® (synthetic conjugated estrogens, A) were updated to include anaphylactic reactions and angioedema.[55] Contraindication labeling was also added to Estrasorb®, Evamist®, and Enjuvia® (synthetic conjugated estrogens, B) for known protein C, protein S, antithrombin deficiency or other thrombophilic disorders.[55]

In March 2015, the contraindications labeling for Cenestin® was also updated to include known or suspected pregnancy. Labeling states, "there is no indication for Cenestin® in pregnancy. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins from oral contraceptives inadvertently during early pregnancy."[55]

In 2015, safety labeling for Estrasorb® and Enjuvia® was updated for the boxed warning of endometrial cancer, cardiovascular disorders, breast cancer and probable dementia. Warnings were edited to emphasize that women with a uterus who use unopposed estrogens have an increased risk of endometrial cancer.[55] Labeling also advises that estrogen alone or in combination with progestins should not be used for the prevention of cardiovascular disease or dementia.[55] Results from the WHI demonstrate an increased risk of stroke and VTE with estrogen alone and increased risk of VTE, stroke, and MI with combination therapy.[55] Results from WHI Memory Study demonstrate an increased risk of probable dementia in postmenopausal women greater than 65 years of age.[55] Warnings also included data from the WHI estrogen plus progestin study which reported an increased risk of invasive breast cancer.[55]

New Formulations or Indications:

No new estrogen or progestin formulations identified.

Randomized Controlled Trials:

No new RCTs were identified. A total of 418 citations were manually reviewed from the literature search. Only trials reporting new comparative evidence were considered for inclusion. After manual review all trials were excluded due to wrong study design, comparator, outcome studied, or lack of reported comparative outcome data.

NEW DRUG EVALUATION:

See **Appendix 2** for **Highlights of Prescribing Information** from the manufacturer, including Black Boxed Warning and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Ospemifene was approved primarily on the basis of 2 phase 3 clinical trials (Studies 15-50310 and 15-50821) which examined the efficacy of ospemifene for the treatment of moderate to severe dyspareunia and vaginal dryness in women with vulvar and vaginal atrophy as a result of menopause[26-28] Therapy was given in addition to background therapy of as needed vaginal lubricants. Women who were on concomitant HRT were excluded from these studies or were required to undergo a washout period before screening[26-28] The number of patients who had previously taken HRT was not reported. A third phase 3 trial was not considered for FDA approval as it did not assess improvement in symptoms.[2] Further extension studies from these trials provided additional efficacy and safety data for up to 12 months. The following primary outcomes were reported as a change from baseline to 12 weeks: vaginal pH, severity of the most bothersome symptom, percent of superficial cells, and percent of parabasalar cells upon vaginal smear.[2]

Overall, the phase 3 trials used for FDA approval had a low to moderate risk of bias. These studies were randomized, double-blinded, placebo-controlled trials. The methods used to randomize patients were not reported but baseline characteristics were balanced in both studies. Matching placebo was used to blind patients, but blinding methods of providers and outcome assessors for vaginal smears was not stated. Attrition was comparable between groups; the most common reasons for discontinuation were adverse effects and withdrawal from the study.[2] Missing data were imputed using last observation carried forward which may overestimate treatment effect if symptoms typically return after treatment discontinuation. The studies were funded by QuatRx Pharmaceuticals and Shionogi, Inc. who developed and market the medication.[26-28]

The majority of women included in these trials were postmenopausal Caucasian women with an average age of 58 to 59 years.[26-28] Women included in the study had a diagnosis of vulvovaginal atrophy defined as superficial cells of less than 5% on a vaginal smear, vaginal pH greater than 5, and at least 1 moderate to severe vaginal symptom.[26-28] Symptom severity was assessed on a 4-point scale with moderate or severe symptoms corresponding to a score of 2 or 3. Exclusion criteria limit ospemifene use in patients with history of endocrine cancer, abnormal gynecological findings upon exam, or in combination with strong CYP 3A4 inhibitors.

Approval for ospemifene was based on symptomatic improvement from baseline to 12 weeks in a modified intention-to-treat (mITT) population including only patients who met *all* the pre-specified inclusion criteria of vulvovaginal atrophy (i.e. superficial cells <5% on vaginal smear, pH >5, and at least one moderate to severe symptom of dyspareunia or vaginal dryness). Patients who did not meet these criteria (1-7% of the population) were excluded from the FDA analysis.[2] Improvement in symptoms was measured on a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). Other endpoints including change in superficial cells, parabasal cells and vaginal pH were not considered clinically meaningful outcomes.[2] In both phase 3 trials, ospemifene 60 mg demonstrated a statistically significant mean reduction in dyspareunia symptoms compared to placebo on a 4-point scale. In the modified intention-to-treat population of Study 15-50310, dyspareunia improved an average of 1.39 points (SD 0.11) in the ospemifene group compared to a 0.89 point (SD 0.11) improvement in the placebo group (MD 0.51, 95% CI 0.20 to 0.81, p=0.0012).[2,3] In Study 15-50821, average improvement in dyspareunia symptoms was 1.55 points (SD 0.06) in the ospemifene groups compared to 1.29 points (SD 0.07) in the placebo group (MD 0.36, 95% CI 0.18 to 0.53, p<0.001).[3] Improvement in vaginal dryness achieved statistical significance in only one study (15-50310), with a difference of 1.29 points (SD 0.09) in the ospemifene 60 mg group compared to 0.92 points (SD 0.10) in the

placebo group (MD 0.37, 95% CI 0.11 to 0.63, p=0.0136).[3] In Study 15-50821, ospemifene failed to achieve statistical significance for the improvement of vaginal dryness (mean change in ospemifene group of 1.33 (SD 0.08) vs. 1.11 (SD 0.08) in placebo; (MD 0.22, 95% CI 0.003 to 0.44, p=0.0853).[3] Similar effect sizes were observed in the intention-to-treat population conducted by the manufacturers.[26-28] Having failed to reach statistical significance in both trials, improvement in vaginal dryness was not included in the FDA indication.

However, despite the fact that ospemifene demonstrates a statistically significant change in dyspareunia, questions remain about its efficacy. In these trials a large placebo response was observed with a mean improvement in symptoms of 0.89 and 1.2 points. This large placebo response may be attributed to the use of background lubricants which participants could use as needed. Overall, rates of lubricant use in both placebo and ospemifene groups decreased with time. In patients taking ospemifene, 22-35% of patients in the ospemifene groups and 29-39% of patients in placebo groups were using non-hormonal lubricant at 12 weeks. Statistical significance was not reported. In addition, the 4-point scale utilized in the trials has not been validated as an assessment tool for evaluation of menopause symptoms, and the minimum clinically important difference with this scale has not been established.

Clinical Safety:
Safety analyses were conducted in 2654 participants included in double-blind phase 2 and 3 trials who received at least one dose of ospemifene. Extension studies of phase 3 trials evaluating ospemifene use for up to 1 year were also included in the safety analysis. A total of 1242 received the FDA approved dose of 60 mg.[2] Secondary analyses conducted with all patients in phase 1, 2, and 3 trials demonstrated similar trends.[2] Serious adverse effects were reported in 39 patients (2.3%) taking ospemifene 30 or 60 mg doses and in 17 patients (1.8%) taking placebo.[2] No serious adverse occurred more in more than 2 subjects per group. Respective serious adverse events that occurred more than once in patients taking ospemifene compared to placebo included appendicitis (2 vs. 0), cerebrovascular accident (2 vs. 1), diverticulitis (2 vs. 1) and DVT (2 vs. 0).[2] Discontinuation due to adverse events was higher in the treatment group (7.1%) compared to placebo (3.7%).[2] Most common adverse events leading to treatment discontinuation were hot flashes, headaches and nausea. The most common adverse events reported in patients taking ospemifene included hot flashes (7.5%), vaginal discharge (3.7%), and headache (3.1%).[2] Additional adverse reactions that have been potentially identified through post-marketing experience include hypersensitivity reactions, angioedema, rash and urticaria.[56]

Assessments for long-term safety outcomes of endometrial, cardiovascular and breast cancer risk included patients in 3 long-term studies with mean follow-up times of approximately 36, 44, and 46 weeks.[2] Assessment of endometrial and uterine safety outcomes demonstrated an increase in endometrial thickness without reports of hyperplasia or carcinoma. Only one case of endometrial hyperplasia without atypia was documented in a patient taking ospemifene 3 months after treatment discontinuation.[2] In phase 2 and 3 trials, endometrial thickness greater than 4 mm was documented in 16.6% of women taking ospemifene 60 mg compared to 5.1% of women taking placebo.[2] Uterine polyps were identified in 10 patients (1.1%) taking 60 mg ospemifene versus 2 patients (0.35%) on placebo.[2] Overall, endometrial adverse effects were consistent with rates in postmenopausal women and demonstrate the agonist effects of ospemifene in the endometrium and uterus.[2] Thromboembolic events (including cerebrovascular accident, DVT, acute MI, cerebral hemorrhage and hemorrhagic stroke) occurred in 6 (0.34%) patients taking ospemifene versus 1 (0.1%) in placebo.[2] Estimated risk of VTE was 2.12 VTEs/1000 patient years, similar to rates observed with other SERMs and low-dose estrogen products.[2] Similar to estrogen products, warnings for increased risk of DVT, stroke and endometrial cancer are included in a box warning for ospemifene. Rates of breast cancer were rare in either group (n=3) and no difference in those treated with ospemifene versus placebo was found.[2] Other serious adverse events included vaginal bleeding or spotting in women with a uterus (17 patients [1.5%] in ospemifene groups vs. 5 patients [0.9%] in placebo groups), urinary symptoms or infection (161 patients [9.5%] on ospemifene vs. 60 [6.3%] on placebo), and pelvic organ prolapse (3 events in ospemifene groups vs. 1 in placebo).[2] Overall, studies of ospemifene conducted for almost 1 year demonstrated a numerically higher rate of serious adverse events indicating a potential increased risk for VTE, breast or endometrial cancer, and cardiovascular events. However, as these events are rare, long-term studies with a larger population of patients to evaluate risk and safety will need to be conducted.

Pharmacology and Pharmacokinetic Properties:[21,56]

Parameter	
Mechanism of Action	Mixed estrogen receptor agonist/antagonist with tissue selective effects. In the vagina, ovaries, and bone, ospemifene acts as an agonist. In the endometrium and mammary glands, ospemifene has antagonist effects.[2]
Absorption	Bioavailability increases when taken with food (T_{max}= 2-2.5 hours)
Distribution and Protein Binding	Volume of distribution is approximately 448 L 99% protein bound
Metabolism	Primarily metabolized via CYP3A4, CYP2C9 and CYP2C19; weak inhibitor of CYP2B6, CYP2C9, CYP2C19, CYP2C8, CYP2D6, and CYP3A4
Half-Life	26 hours
Elimination	75% in feces, 7% in urine

Abbreviations: T_{max} = time to maximum concentration

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:

1) Improvement or resolution of vaginal symptoms (sexual dysfunction, vaginal dryness, discharge, itching, and dyspareunia)
2) Health-related quality of life
3) Early study withdrawal due to adverse event(s)
4) Serious adverse effects

Primary Study Endpoints:

1) Change in symptom severity (dyspareunia and vaginal dryness)
2) Change in superficial cells on vaginal smear
3) Change in parabasal cells on vaginal smear
4) Change in vaginal pH

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. Bachmann, et al.[26] FDA Summary Review[2] Study #: 15-50310 Phase 3, MC, DB, PC, RCT	1. Ospemifene 30 mg daily 2. Ospemifene 60 mg daily 3. Placebo 1:1:1 12 weeks	Demographics: - Mean age: 58.6 years - White: 99% - Time since last menstrual period: 15 years - Hysterectomy: 54.1% - Proportion w/dyspareunia: 46%; Mean baseline severity: 2.6 - Proportion w/vaginal dryness: 39%; Mean baseline severity: 2.4 Key Inclusion Criteria: - Postmenopausal women* - Age 40-80 years - VVA (superficial cells <5% on vaginal smear, pH >5, and ≥1 moderate to severe symptom) - Moderate to severe dyspareunia or vaginal dryness (score >2) Key Exclusion Criteria: - Endometrial thickness >4 mm - Pathological findings on endometrial exam or other gynecological abnormalities - Suspicion of malignancy or history of malignancy within 10 years - Abnormal labs, ECG, mammogram, breast or physical exam - History or current blood or thromboembolic disorder - BMI >37 kg/m^2 - BP >180/100 mmHg - Severe renal or hepatic impairment - Alcohol >14 drinks/week	ITT: 1. 282 2. 276 3. 268 mITT (patients meeting all 3 criteria for VVA):[2] 1. NR 2. 223 3. 223 Attrition: 1. 20.2% 2. 15.2% 3. 14.2%	Primary Endpoints at 12 weeks (ITT population): Change in vaginal dryness (0-3 scale): mean (SD NR) 1. 1.22 (p=0.04 vs. PBO) 2. 1.26 (p=0.021 vs. PBO) 3. 0.84 Change in dyspareunia (0-3 scale): mean (SD NR) 1. 1.02 (p=NS vs. PBO) 2. 1.19 (p=0.023 vs. PBO) 3. 0.89 Secondary Endpoints: Proportion of patients using non-hormonal lubricant at 12 weeks: 1. 31% 2. 22% 3. 29% p-values NR	 NA NA NA	Serious ADE: 1. 5 (1.8%) 2. 0 (0.0%) 3. 4 (1.5%) p-values NR DC due to ADE: 1. 15 (5.3%) 2. 13 (4.7%) 3. 13 (4.9%) p-values NR Change in endometrial thickness: mean (SD) 1. 0.42 (1.35) mm 2. 0.72 (1.59) mm 3. -0.02 (1.03) mm p-values NR	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: UNCLEAR. Randomization method and allocation concealment NR. Baseline characteristics were balanced. Performance Bias: LOW. Patients blinded via matching placebo. Specific blinding of providers NR. Detection Bias: HIGH. Patients were blinded, but subjective assessment of symptomatic outcomes increases risk of bias. Blinding of assessors for vaginal smears NR. Endometrial biopsies assessed by 2 independent blinded pathologists. Attrition Bias: HIGH. Overall attrition was high (14-20%) but comparable between groups; reasons for discontinuation were NR. LOCF was used for missing values which may increase magnitude of treatment effect. Analysis of ITT and PP populations, but not mITT suggested by the FDA. Power assumptions were NR. Reporting Bias: HIGH. Measures of variance NR leading to uncertain effect size. Funding for studies provided by QuatRx Pharmaceuticals; manuscript funding provided by Shionogi, Inc. **Applicability**: Patient: Majority of patients were Caucasian limiting applicability to other populations. Older population with an average 15 years since menopause onset. Efficacy and safety in a younger population or patients with less severe symptoms is unclear. The number of patients who were on HRT prior to enrollment in the study was not reported. Intervention: Background use of lubricant and large placebo response makes assessment of magnitude of effect difficult. Comparator: Placebo adequate. Lack of active control makes place in therapy less clear. Outcomes: Surrogate outcomes of vaginal pH and change in endometrial cells upon exam with unclear correlation to symptom improvement. Minimum clinically significant difference with use of a 4 point Likert scale for MBS is unclear. Safety evaluated in an extension study for up to 52 weeks, but duration

		- Concurrent HRT, strong CYP 3A4 inhibitors, or digitalis alkaloids						may be inadequate to evaluate long-term safety data for endometrial or cardiovascular outcomes. Setting: 76 centers in the United States.
2. Portman, et al. 2013. [27] FDA Summary Review[2] Study #: 15-50821 Phase 3, MC, DB, PC, RCT Results are reported separately for patients with dyspareunia and patients with vaginal dryness as their MBS (see Portman, et al, 2014).	1. Ospemifene 60 mg daily 2. Placebo 1:1 12 weeks	Demographics: - Mean age: 58.1 years - White: 90.6% - Mean baseline symptom severity score: 2.7 Key Inclusion Criteria: - See Study 15-50310 - MBS is moderate to severe dyspareunia (score >2) Key Exclusion Criteria: - See Study 15-50310 - Other gynecological abnormalities including uterine bleeding, polyps, uterine fibroids >3 cm, or vaginal infection requiring medication - History of cerebrovascular incidents	ITT: 1. 303 2. 302 PP: 1. 255 2. 251 mITT (patients meeting all 3 criteria for VVA):[2] 1. 301 2. 297 Attrition: 1. 25 (8.3%) 2. 36 (11.9%)	Primary Endpoints at 12 weeks (ITT population): Change in dyspareunia (0-3 scale): Mean (SD) 1. -1.5 (1.1) 2. -1.2 (1.1) p=0.0001 Secondary Endpoints: Proportion of patients using non-hormonal lubricant at 12 weeks: 1. 35.1% 2. 39.3% p-value NR	NA NA	Serious ADE: 1. 4 (1.3%) 2. 4 (1.3%) p-value NR DC due to ADE: 1. 14 (4.6%) 2. 9 (3.0%) p-value NR Change in Endometrial Thickness: mean (SD) 1. 0.40 (1.25) mm 2. 0.10 (1.29) mm p-value NR	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: UNCLEAR. See Study 15-50310. Performance Bias: LOW. Patients blinded via matching placebo. Specific blinding of providers NR. Detection Bias: HIGH. Patients were blinded, but subjective assessment of symptomatic outcomes increases risk of bias. Blinding of assessors for vaginal smears was NR. Endometrial biopsies assessed by 2 central blinded independent pathologists. Disagreements resolved by a 3rd pathologist. Power assumptions were NR. Attrition Bias: LOW. Similar attrition between groups (<5%). Missing data imputed using LOCF which may result in overestimation of treatment effect. Analysis conducted in both ITT and PP populations with similar results. Reporting Bias: LOW. Study funded by QuatRx Pharmaceuticals; manuscript funded by Shionogi, Inc. **Applicability**: Patient: See Study 15-50310. Intervention: See Study 15-50310. Comparator: See Study 15-50310. Outcomes: Wide standard deviations demonstrate imprecise estimate of treatment effect. Minimum clinically important difference for MBS is unclear with use of a 0-3 scale. Setting: 110 sites in the United States from August 2008 to July 2009.
3. Portman, et al, 2014.[28] FDA Summary Review[2] Study #: 15-50821 Phase 3, MC, DB, PC, RCT	1. Ospemifene 60 mg daily 2. Placebo 1:1 12 weeks	Demographics: - Mean age: 59.6 year - White: 81.8% - Mean baseline symptom severity NR Key Inclusion Criteria: - See Study 15-50310. - MBS is moderate to severe vaginal dryness (score >2) Key Exclusion Criteria: - See Portman, et al. 2013.	ITT: 1. 160 2. 154 mITT (patients meeting all 3 criteria for VVA):[2] 1. 157 2. 150 PP:	Primary Endpoints at 12 weeks (ITT population): Change in Vaginal Dryness (0-3 scale): mean (SD) 1. -1.3 (1.08) 2. -1.1 (1.02) p = 0.08 Secondary endpoints: Proportion of patients using non-hormonal lubricant at 12 weeks	NA NA	Serious ADE: 1. 2 (1.3%) 2. 3 (1.9%) p-values NR DC due to ADE: 1. 12 (7.5%) 2. 5 (3.2%) p-values NR Change in Endometrial	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: UNCLEAR. See Study 15-50310 Performance Bias: LOW. See Portman, et al. 2013. Detection Bias: HIGH. See Portman, et al. 2013. Attrition Bias: LOW. See Portman, et al. 2013. Reporting Bias: HIGH. Baseline values for primary endpoints NR. Emphasis placed on post-hoc evaluation of "responders" and percent of patients who had a large change in symptom score. Study funded by QuatRx Pharmaceuticals; manuscript funded by Shionogi, Inc. **Applicability**:

Results are reported separately for patients with dyspareunia and patients with vaginal dryness as their MBS (see Portman, et al, 2013).			1. 127 2. 137 Attrition: 1. 22 (13.8%) 2. 17 (11.0%)	1. 21.7% 2. 33.0% p-value NR		Thickness: mean (SD) 1. 0.82 (1.68) mm 2. -0.11 (1.20) mm p-values NR		Patient: See Study 15-50310. Intervention: See Study 15-50310. Comparator: See Study 15-50310. Outcomes: Wide standard deviations indicate imprecise estimate of treatment effect. Minimum clinically important difference for MBS is unclear with use of a 4 point scale. Setting: See Portman, et al. 2013.
Abbreviations: ADE = adverse drug events; ARR = absolute risk reduction; BMI = body mass index; BP = blood pressure; CI = confidence interval; DC = discontinuation; DB = double-blinded; ECG = electrocardiogram; HRT = hormone replacement therapy; ITT = intention to treat; LOCF = last observation carried forward; MBS = most bothersome symptom; 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; PBO = placebo; PC = placebo controlled; PP = per protocol; RCT = randomized control trial; SD = standard deviation; VVA = vulvovaginal atrophy *Post-menopause was defined as >12 months since last spontaneous menstrual bleeding, >6 weeks since bilateral oophorectomy, or FSH >40 IU/L in women with hysterectomy and intact ovaries.								

References:

1. Grant MD, Piper M, Bohlius J, et al. Menopausal Symptoms: Comparative Effectiveness of Therapies. Comparative Effectiveness Reviews, No. 147. (Prepared by Blue Cross and Blue Shield Association Technology Evaluation Center Evidence-based Practice Center under Contract No. 290-2007-10058-I.) AHRQ Publication No. 15-EHC005-EF. Rockville, MD: Agency for Healthcare Research and Quality; March 2015. www.effectivehealthcare.ahrq.gov/reports/final.cfm.
2. Ospemifene Summary Review. US Food and Drug Administration Center for Drug Evaluation and Research. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203505Orig1s000SumR.pdf. Accessed August 8, 2016.
3. Ospemifene Statistical Review. US Food and Drug Administration Centers for Drug Evaluation and Research. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203505Orig1s000StatR.pdf. Accessed December 2, 2016.
4. National Collaborating Centre for Women's and Children's Health. Menopause. London: National Institute for Health and Care Excellence (UK). 2015; Available from http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0079648/.
5. Xu Y, Lin J, Wang S, Xiong J, Zhu Q. Combined estrogen replacement therapy on metabolic control in postmenopausal women with diabetes mellitus. *The Kaohsiung Journal of Medical Sciences.* 2014;30(7):350-361.
6. Shim SH, Lee SJ, Kim SN. Effects of hormone replacement therapy on the rate of recurrence in endometrial cancer survivors: a meta-analysis. *Eur J Cancer.* 2014;50(9):1628-1637.
7. Li D, Ding CY, Qiu LH. Postoperative hormone replacement therapy for epithelial ovarian cancer patients: a systematic review and meta-analysis. *Gynecol Oncol.* 2015;139(2):355-362.
8. Brown J, Farquhar C. Endometriosis: an overview of Cochrane Reviews. *Cochrane Database Syst Rev.* 2014(3):Cd009590.
9. Practice bulletin no. 114: management of endometriosis. *Obstet Gynecol.* 2010;116(1):223-236.
10. Leyland N, Casper R, Laberge P, et al. Endometriosis: Diagnosis and Management. *Journal of Obstetrics and Gynaecology Canada.* 2010;32(7):S1-S3.
11. Lethaby A, Hussain M, Rishworth JR, Rees MC. Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding. *Cochrane Database Syst Rev.* 2015;4:CD002126.
12. Matteson KA, Rahn DD, Wheeler TL, 2nd, et al. Nonsurgical management of heavy menstrual bleeding: a systematic review. *Obstet Gynecol.* 2013;121(3):632-643.
13. Hoaglin DC, Filonenko A, Glickman ME, Wasiak R, Gidwani R. Use of mixed-treatment-comparison methods in estimating efficacy of treatments for heavy menstrual bleeding. *Eur J Med Res.* 2013;18:17.
14. Gallos ID, Yap J, Rajkhowa M, Luesley DM, Coomarasamy A, Gupta JK. Regression, relapse, and live birth rates with fertility-sparing therapy for endometrial cancer and atypical complex endometrial hyperplasia: a systematic review and metaanalysis. *Am J Obstet Gynecol.* 2012;207(4):266.e261-212.
15. Baker J, Obermair A, Gebski V, Janda M. Efficacy of oral or intrauterine device-delivered progestin in patients with complex endometrial hyperplasia with atypia or early endometrial adenocarcinoma: a meta-analysis and systematic review of the literature. *Gynecol Oncol.* 2012;125(1):263-270.
16. Dodd JM, Jones L, Flenady V, Cincotta R, Crowther CA. Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth. *Cochrane Database Syst Rev.* 2013(7):Cd004947.
17. Conde-Agudelo A, Romero R, Nicolaides K, et al. Vaginal progesterone vs. cervical cerclage for the prevention of preterm birth in women with a sonographic short cervix, previous preterm birth, and singleton gestation: a systematic review and indirect comparison metaanalysis. *Am J Obstet Gynecol.* 2013;208(1):42.e41-42.e18.

18. Romero R, Nicolaides K, Conde-Agudelo A, et al. Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: a systematic review and metaanalysis of individual patient data. *Am J Obstet Gynecol.* 2012;206(2):124.e121-119.
19. Likis FE, Edwards DR, Andrews JC, et al. Progestogens for preterm birth prevention: a systematic review and meta-analysis. *Obstet Gynecol.* 2012;120(4):897-907.
20. Saccone G, Khalifeh A, Elimian A, et al. Vaginal progesterone compared to intramuscular 17-alpha-hydroxyprogesterone caproate for prevention of recurrent spontaneous preterm birth in singleton gestations: a systematic review and meta-analysis of randomized controlled trials. *Ultrasound Obstet Gynecol.* 2016; E-published ahead of print.
21. Micromedex Healthcare Series [internet database]. Greenwood Village, CO: Truven Health Analytics, Inc. Updated periodically. Accessed July 29, 2016.
22. Sentena K. Class Review: Cross-sex Hormone Therapy. *Oregon State University Drug Use Research & Management Program.* 2015.
23. DynaMed [internet database]. Ipswich, MA: EBSCO Publishing. Updated July 22, 2016. Accessed September 7, 2016.
24. Stuenkel CA, Davis SR, Gompel A, et al. Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2015;100(11):3975-4011.
25. Chlebowski RT, Anderson GL, Sarto GE, et al. Continuous Combined Estrogen Plus Progestin and Endometrial Cancer: The Women's Health Initiative Randomized Trial. *J Natl Cancer Inst.* 2016;108(3).
26. Bachmann GA, Komi JO, Ospemifene Study G. Ospemifene effectively treats vulvovaginal atrophy in postmenopausal women: results from a pivotal phase 3 study. *Menopause.* 2010;17(3):480-486.
27. Portman DJ, Bachmann GA, Simon JA, Ospemifene Study G. Ospemifene, a novel selective estrogen receptor modulator for treating dyspareunia associated with postmenopausal vulvar and vaginal atrophy. *Menopause.* 2013;20(6):623-630.
28. Portman D, Palacios S, Nappi RE, Mueck AO. Ospemifene, a non-oestrogen selective oestrogen receptor modulator for the treatment of vaginal dryness associated with postmenopausal vulvar and vaginal atrophy: a randomised, placebo-controlled, phase III trial. *Maturitas.* 2014;78(2):91-98.
29. Caillouette JC, Sharp CF, Jr., Zimmerman GJ, Roy S. Vaginal pH as a marker for bacterial pathogens and menopausal status. *Am J Obstet Gynecol.* 1997;176(6):1270-1275; discussion 1275-1277.
30. Roy S, Caillouette JC, Roy T, Faden JS. Vaginal pH is similar to follicle-stimulating hormone for menopause diagnosis. *Am J Obstet Gynecol.* 2004;190(5):1272-1277.
31. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/results?term=ospemifene&Search=Search. Accessed October 18, 2016.
32. Oregon State University Drug Use Resarch and Management Program. New Drug Evaluation: 17 alpha-hydroxyprogesterone caproate. 2013.
33. Felix Wong WS, Danforn Lim CE. Hormonal treatment for endometriosis associated pelvic pain. *Iran J Reprod Med.* 2011;9(3):163-170.
34. Singh S BC, Dunn S, Leyland N, Wolfman WL. Clinical Practice Gynaecology Committee. Abnormal uterine bleeding in pre-menopausal women. *J Obstet Gynaecol Can.* (35(5 eSuppl)):S1-28.
35. Shaw ST, Jr., Aaronson DE, Moyer DL. Quantitation of menstrual blood loss--further evaluation of the alkaline hematin method. *Contraception.* 1972;5(6):497-513.
36. Hald K, Lieng M. Assessment of periodic blood loss: interindividual and intraindividual variations of pictorial blood loss assessment chart registrations. *J Minim Invasive Gynecol.* 2014;21(4):662-668.
37. Reid PC, Coker A, Coltart R. Assessment of menstrual blood loss using a pictorial chart: a validation study. *BJOG.* 2000;107(3):320-322.
38. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Uterine Neoplasms Version 2.2016. https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf. Accessed September 7, 2016.
39. Alberta Health Services. Endometrial Cancer. Clinical Practice Guideline Gyne-002. Version 5. 2015.

40. Lexicomp [internet database]. Hudson, OH: Wolters Kluwer. Updated periodically. Accessed August 5, 2016.
41. Gu H, Zhao X, Zhao X, Yang Y, Lv X. Risk of stroke in healthy postmenopausal women during and after hormone therapy: a meta-analysis. *Menopause.* 2014;21(11):1204-1210.
42. Boardman HM, Hartley L, Eisinga A, et al. Hormone therapy for preventing cardiovascular disease in post-menopausal women. *Cochrane Database Syst Rev.* 2015;3:CD002229.
43. Corbelli J, Shaikh N, Wessel C, Hess R. Low-dose transdermal estradiol for vasomotor symptoms: a systematic review. *Menopause.* 2015;22(1):114-121.
44. Gaudard AMIS, Silva de Souza S, Puga MES, Marjoribanks J, da Silva EMK, Torloni MR. Bioidentical hormones for women with vasomotor symptoms. *Cochrane Database Syst Rev.* 2016(8).
45. Rahn DD, Carberry C, Sanses TV, et al. Vaginal estrogen for genitourinary syndrome of menopause: a systematic review. *Obstet Gynecol.* 2014;124(6):1147-1156.
46. Canadian Agency for Drugs and Technologies in Health. Oral Progesterone for the Treatment of Menopausal Symptoms: A Review of the Clinical Evidence. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2014.
47. Abu Hashim H, Ghayaty E, El Rakhawy M. Levonorgestrel-releasing intrauterine system vs oral progestins for non-atypical endometrial hyperplasia: a systematic review and metaanalysis of randomized trials. *Am J Obstet Gynecol.* 2015;213(4):469-478.
48. Sotiriadis A, Papatheodorou S, Makrydimas G. Perinatal outcome in women treated with progesterone for the prevention of preterm birth: a meta-analysis. *Ultrasound Obstet Gynecol.* 2012;40(3):257-266.
49. National Collaborating Centre for Women's and Children's Health. Preterm Labour and Birth. London: National Institute for Health and Care Excellence (UK). 2015 [cited 2016 Sept 7]; Available from http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0080792/.
50. Canadian Agency for Drugs and Technologies in Health. Vaginal Micronized Progesterone Capsules for the Prevention of Miscarriage and Preterm Birth: A Review of the Clinical Evidence. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2014.
51. Schuit E, Stock S, Rode L, et al. Effectiveness of progestogens to improve perinatal outcome in twin pregnancies: an individual participant data meta-analysis. *BJOG.* 2015;122(1):27-37.
52. National Collaborating Centre for Women's and Children's Health (UK). Heavy Menstrual Bleeding. London: National Institute for Health and Care Excellence (UK). 2007; Available from https://www.ncbi.nlm.nih.gov/books/NBK56536/.
53. Practice bulletin no. 136: management of abnormal uterine bleeding associated with ovulatory dysfunction. *Obstet Gynecol.* 2013;122(1):176-185.
54. National Institute for Health and Care Excellence. Multiple pregnancy: antenatal care for twin and triplet pregnancies. London: National Institute for Health and Care Excellence (UK). 2011; Available from www.nice.org.uk/Guidance/CG129.
55. Food and Drug Administration. Medical Product Safety Information. http://www.fda.gov/Safety/MedWatch/SafetyInformation/default.htm. Accessed October 14, 2016.
56. Ospemifene (Osphena) film coated tablet [package insert]. Florham Park, NJ: Shionogi Inc; 2015.

ESTROGEN REPLACEMENT, ORAL

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	TABLET	ESTRACE	ESTRADIOL	Y
ORAL	TABLET	ESTRADIOL	ESTRADIOL	Y
ORAL	TABLET	ESTROPIPATE	ESTROPIPATE	Y
ORAL	TABLET	ANGELIQ	DROSPIRENONE/ESTRADIOL	N
ORAL	TABLET	COVARYX	ESTROGEN,ESTER/ME-TESTOSTERONE	N
ORAL	TABLET	COVARYX H.S.	ESTROGEN,ESTER/ME-TESTOSTERONE	N
ORAL	TABLET	DUAVEE	ESTROGENS,CONJ/BAZEDOXIFENE	N
ORAL	TABLET	EEMT	ESTROGEN,ESTER/ME-TESTOSTERONE	N
ORAL	TABLET	EEMT H.S.	ESTROGEN,ESTER/ME-TESTOSTERONE	N
ORAL	TABLET	ENJUVIA	ESTROGENS,CONJ.,SYNTHETIC B	N
ORAL	TABLET	ESTRADIOL-NORETHINDRONE ACETAT	ESTRADIOL/NORETHINDRONE ACET	N
ORAL	TABLET	ESTROGEN & METHYLTESTOSTERONE	ESTROGEN,ESTER/ME-TESTOSTERONE	N
ORAL	TABLET	ESTROGEN-METHYLTESTOSTERONE	ESTROGEN,ESTER/ME-TESTOSTERONE	N
ORAL	TABLET	FEMHRT	NORETHINDRONE AC-ETH ESTRADIOL	N
ORAL	TABLET	FYAVOLV	NORETHINDRONE AC-ETH ESTRADIOL	N
ORAL	TABLET	JEVANTIQUE LO	NORETHINDRONE AC-ETH ESTRADIOL	N
ORAL	TABLET	JINTELI	NORETHINDRONE AC-ETH ESTRADIOL	N
ORAL	TABLET	LOPREEZA	ESTRADIOL/NORETHINDRONE ACET	N
ORAL	TABLET	MENEST	ESTROGENS,ESTERIFIED	N
ORAL	TABLET	MIMVEY	ESTRADIOL/NORETHINDRONE ACET	N
ORAL	TABLET	MIMVEY LO	ESTRADIOL/NORETHINDRONE ACET	N
ORAL	TABLET	NORETHINDRON-ETHINYL ESTRADIOL	NORETHINDRONE AC-ETH ESTRADIOL	N
ORAL	TABLET	PREFEST	ESTRADIOL/NORGESTIMATE	N
ORAL	TABLET	PREMARIN	ESTROGENS, CONJUGATED	N
ORAL	TABLET	PREMPHASE	ESTROGEN,CON/M-PROGEST ACET	N
ORAL	TABLET	PREMPRO	ESTROGEN,CON/M-PROGEST ACET	N

ESTROGEN REPLACEMENT, TRANSDERMAL

ROUTE	FORMULATION	BRAND	GENERIC	PDL
TRANSDERM	PATCH TDSW	ALORA	ESTRADIOL	Y
TRANSDERM	PATCH TDSW	ESTRADIOL	ESTRADIOL	Y
TRANSDERM	PATCH TDSW	MINIVELLE	ESTRADIOL	Y
TRANSDERM	PATCH TDSW	VIVELLE-DOT	ESTRADIOL	Y
TRANSDERM	PATCH TDWK	CLIMARA	ESTRADIOL	Y
TRANSDERM	PATCH TDWK	ESTRADIOL	ESTRADIOL	Y
TRANSDERM	GEL MD PMP	ELESTRIN	ESTRADIOL	N
TRANSDERM	GEL PACKET	DIVIGEL	ESTRADIOL	N
TRANSDERM	PATCH TDSW	COMBIPATCH	ESTRADIOL/NORETHINDRONE ACET	N
TRANSDERM	PATCH TDWK	CLIMARA PRO	ESTRADIOL/LEVONORGESTREL	N
TRANSDERM	PATCH TDWK	MENOSTAR	ESTRADIOL	N
TRANSDERM	SPRAY	EVAMIST	ESTRADIOL	N

ESTROGEN REPLACEMENT, VAGINAL

ROUTE	FORMULATION	BRAND	GENERIC	PDL
VAGINAL	CREAM/APPL	PREMARIN	ESTROGENS, CONJUGATED	Y
VAGINAL	TABLET	VAGIFEM	ESTRADIOL	Y
VAGINAL	TABLET	VAGIFEM	ESTRADIOL	Y
VAGINAL	CREAM/APPL	ESTRACE	ESTRADIOL	N
VAGINAL	CREAM/APPL	ESTRACE	ESTRADIOL	N
VAGINAL	VAG RING	ESTRING	ESTRADIOL	N
VAGINAL	VAG RING	ESTRING	ESTRADIOL	N
VAGINAL	VAG RING	FEMRING	ESTRADIOL ACETATE	N
VAGINAL	VAG RING	FEMRING	ESTRADIOL ACETATE	N

PROGESTINS

ROUTE	FORMULATION	BRAND	GENERIC	PDL
INTRAMUSC	VIAL	HYDROXYPROGESTERONE CAPROATE	HYDROXYPROGESTERONE CAPROATE	Y
INTRAMUSC	VIAL	MAKENA	HYDROXYPROGESTERONE CAPROATE	Y
ORAL	TABLET	MEDROXYPROGESTERONE ACETATE	MEDROXYPROGESTERONE ACETATE	
ORAL	TABLET	PROVERA	MEDROXYPROGESTERONE ACETATE	
ORAL	TABLET	NORETHINDRONE ACETATE	NORETHINDRONE ACETATE	
ORAL	TABLET	AYGESTIN	NORETHINDRONE ACETATE	
INTRAMUSC	VIAL	PROGESTERONE	PROGESTERONE	
VAGINAL	SUPPOSITORY	FIRST-PROGESTERONE VGS	PROGESTERONE	
VAGINAL	INSERT	ENDOMETRIN	PROGESTERONE	
ORAL	CAPSULE	PROGESTERONE	PROGESTERONE, MICRONIZED	
ORAL	CAPSULE	PROMETRIUM	PROGESTERONE, MICRONIZED	
VAGINAL	GEL	CRINONE	PROGESTERONE, MICRONIZED	

Appendix 2: Highlights of Prescribing Information

OSPHENA- ospemifene tablet, film coated
Shionogi Inc.

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

OSPHENA ® (ospemifene) tablets, for oral use
Initial U.S. Approval: 2013

WARNING: ENDOMETRIAL CANCER AND CARDIOVASCULAR DISORDERS

See full prescribing information for complete boxed warning.

OSPHENA is an estrogen agonist/antagonist with tissue selective effects. In the endometrium, OSPHENA has estrogen agonistic effects. There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy reduces the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer *[see Warnings and Precautions (5.2)]*.
Estrogen-alone therapy has an increased risk of stroke and deep vein thrombosis (DVT). OSPHENA 60 mg had cerebral thromboembolic and hemorrhagic stroke incidence rates of 0.72 and 1.45 per thousand women, respectively vs. 1.04 and 0 per thousand women, respectively in placebo. For deep vein thrombosis, the incidence rate for OSPHENA 60 mg is 1.45 per thousand women vs. 1.04 per thousand women in placebo *[see Warnings and Precautions (5.1)]*.

RECENT MAJOR CHANGES

- **CONTRAINDICATIONS** (4) 02/2015

INDICATIONS AND USAGE

OSPHENA is an estrogen agonist/antagonist indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause (1)

DOSAGE AND ADMINISTRATION

- One tablet taken orally once daily with food (2.1)

DOSAGE FORMS AND STRENGTHS

Tablet: 60 mg (3)

CONTRAINDICATIONS

- Undiagnosed abnormal genital bleeding (4)
- Known or suspected estrogen-dependent neoplasia (4, 5.2)
- Active DVT, pulmonary embolism (PE), or a history of these conditions (4, 5.1)
- Active arterial thromboembolic disease (for example, stroke and myocardial infarction [MI]), or a history of these conditions (4, 5.1)
- Hypersensitivity (for example, angioedema, urticaria, rash, pruritus) to OSPHENA or any ingredients (4)
- Known or suspected pregnancy (4, 8.1)

WARNINGS AND PRECAUTIONS

- Venous Thromboembolism: Risk of DVT and pulmonary embolism (5.1)
- Known, suspected, or history of breast cancer (5.2)
- Severe Hepatic Impairment (5.3, 8.7, 12.3)

ADVERSE REACTIONS

Adverse reactions (≥1 percent) include: hot flush, vaginal discharge, muscle spasms, genital discharge, hyperhidrosis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Shionogi Inc. at 1-855-OSPHENA (1-855-677-4362) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Do not use estrogens or estrogen agonist/antagonist concomitantly with OSPHENA (7.1,12.3)
- Do not use fluconazole concomitantly with OSPHENA. Fluconazole increases serum concentrations of OSPHENA (7.2, 12.3)
- Do not use rifampin concomitantly with OSPHENA. Rifampin decreases serum concentration of OSPHENA (7.2, 12.3)

USE IN SPECIFIC POPULATIONS

- Nursing Mothers: It is not known whether OSPHENA is excreted in human breast milk (8.3)

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

Revised: 8/2015

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) 1946 to September Week 4, 2016.

1	exp Menopause/	51731
2	exp Vasomotor System/	16967
3	exp Osteoporosis, Postmenopausal/	11972
4	hypoestrogenism.mp.	381
5	vaginal atrophy.mp.	385
6	vulval atrophy.mp.	3
7	1 or 2 or 3 or 4 or 5 or 6	78449
8	estropipate.mp.	48
9	exp Estrogens/	152946
10	exp Estrogen Replacement Therapy/	14636
11	8 or 9 or 10	161478
12	exp Progestins/	64782
13	exp Norpregnanes/	20040
14	exp Progesterone/	66993
15	12 or 13 or 14	90340
16	exp endometriosis/ or exp endometrial hyperplasia/	21969
17	uterine bleeding.mp. or exp Uterine Hemorrhage/	20507
18	exp Endometrial Neoplasms/	18200
19	11 or 15	205383
20	exp obstetric labor, premature/ or exp premature birth/	21466
21	16 or 17 or 18 or 20	78493
22	7 or 21	153438
23	19 and 22	25646
24	limit 23 to (english language and humans and yr="2014 -Current" and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or pragmatic clinical trial or randomized controlled trial or systematic reviews))	418

Estrogen Derivatives

Goal(s):

- Restrict use to medically appropriate conditions funded under the OHP

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred estrogen derivatives
- All estrogen derivatives for patients <18 years of age

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 estrogen requested for a patient ≥18 years old?	**Yes:** Go to #3	**No**: Go to #4
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a co-pay. Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class and approve for up to 12 months.	**No:** Approve for up to 12 months.
4. Is the medication requested for gender dysphoria (ICD10 F642, F641)?	**Yes:** Go to #5	**No:** Go to #6

Approval Criteria		
5. Have **all** of the following criteria been met? • Patient has the capacity to make fully informed decisions and to give consent for treatment; and • If patient <18 years of age, the prescriber is a pediatric endocrinologist; and • The prescriber agrees criteria in Guideline Notes on the OHP List of Prioritized Services have been met.	**Yes:** Approve for up to 6 months	**No**: Pass to RPh. Deny; medical appropriateness
6. Is the medication requested for hypogonadism?	**Yes:** Approve for up to 6 months	**No**: Go to #7
7. RPh only: All other indications need to be evaluated to see if funded under the OHP.	If funded and prescriber provides supporting literature: Approve for up to 12 months.	If non-funded: Deny; not funded by the OHP

P&T / DUR Review: *11/16 (SS); 11/15 (KS)*
Implementation: *1/1/16*

Conjugated Estrogens/Bazedoxifene (Duavee®)

Goal(s):
- Approve conjugated estrogens/bazedoxifene only for indications where there is evidence to support its use and safety.
- Support the use of agents with clinical efficacy and safety supported by the medical literature and guidelines.

Initiative:
- Prior Authorization

Length of Authorization:
- 6-12 months

Requires PA:
- Conjugated estrogens/bazedoxifene

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/

Step Therapy Required Prior to Coverage:
Prevention of vasomotor symptoms: conventional hormone therapy (see preferred drug list options at (www.orpdl.org)
Prevention of osteoporosis: bisphosphonates (see preferred drug list options at www.orpdl.org).

Approval Criteria		
1. What is the diagnosis?	Record ICD10 code	
2. Is patient a postmenopausal woman within 10 years of menopause?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is the patient <60 years of age with an intact uterus?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
4. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a co-pay. Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #5
5. Is the patient being prescribed the medication for the prevention of osteoporosis?	**Yes:** Go to #6	**No:** Go to #7
6. Has the patient tried and failed, or is there a contraindication to, bisphosphonates?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the medication being prescribed for the prevention of vasomotor symptoms?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Has the patient tried and failed or has a contraindication to conventional hormone therapy?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T Review: *11/14*
Implementation: *1/1/15*

Hydroxyprogesterone caproate (Makena®)

Goal(s):

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

Length of Authorization:

Up to 20 weeks

Requires PA:

- Hydroxyprogesterone caproate injection

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the patient between 16 weeks and 36 weeks 6 days gestation with a singleton pregnancy?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Has the patient had a prior history of preterm delivery before 37 weeks gestation (spontaneous preterm singleton birth)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is treatment being initiated at 16 weeks, 0 days and to 20 weeks, 6 days of gestation?	**Yes:** Approve through week 37 of gestation or delivery, whichever occurs first (no more than 20 doses).	**No:** Pass to RPh. Deny; medical appropriateness

P&T Review: *11/16 (SS); 5/13*
Implementation: *1/1/14*

Drug Use Research & Management Program
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Salem, Oregon 97301-1079
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Class Review: Antidiarrheals

Date of Review: January 2017

Purpose for Class Review:
To identify appropriate utilization management strategies for drugs used to treat diarrhea.

Research Questions:
1. What is the comparative efficacy and effectiveness for bismuth subsalicylate, loperamide, diphenoxylate/atropine, paregoric, crofelemer, or opium tincture in management of diarrhea?
2. What are the comparative harms or potential abuses for bismuth subsalicylate, loperamide, diphenoxylate/atropine, paregoric, crofelemer, or opium tincture?
3. Are there subgroups of patients based on demographics (age, racial or ethnic groups and gender), other medications, or co-morbidities for which one treatment for diarrhea is more effective or associated with fewer adverse events?

Conclusions:
- There is insufficient comparative evidence of efficacy and effectiveness between bismuth subsalicylate, loperamide, diphenoxylate/atropine, paregoric, crofelemer and opium tincture.
- Moderate quality evidence shows that the addition of loperamide to ciprofloxacin for treatment of traveler's diarrhea may decrease the duration of diarrhea within the first 24 to 48 hours of symptom onset.[1]
- Opium tincture has not been evaluated by the United States Food and Drug Administration (FDA) for safety and effectiveness because it was marketed before 1962.[2]
- The FDA recently published a warning about possible cardiac toxicity related to loperamide abuse or misuse at doses greater than 16 mg per day or when used with specific medications that delay loperamide metabolism.[3]
- Paregoric and diphenoxylate/atropine labeling now contain warnings regarding safety issues associated with the entire class of opioid medications.[4]
- Moderate quality evidence reveals that crofelemer is safe and effective in decreasing frequency of diarrhea in HIV-seropositive individuals stable on anti-retroviral therapy.[5]
- Low quality evidence shows that loperamide may decrease duration of diarrhea by 0.8 days as well as decrease stool frequency in children when used as an adjunct to oral or intravenous hydration.[6]

Recommendations:

- Add antidiarrheal medications to the Oregon Health Plan (OHP) fee-for-service practitioner-managed prescription drug plan and designate all drugs as non-preferred to restrict use to only funded conditions under the OHP.
- Add quantity limits to loperamide, diphenoxylate/atropine, and crofelemer to insure safe and appropriate use:
    - Loperamide = maximum 16 mg per 24 hours
    - Diphenoxylate/atropine = maximum 20 mg/0.2 mg per 24 hours
    - Crofelemer = maximum 500 mg per 24 hours

Background:

According to the World Health Organization (WHO), there are about 2 billion cases of diarrheal disease worldwide every year.[7] In the United States (U.S.) alone, an estimated 211–375 million episodes of diarrheal illness occur each year, resulting in 73 million physician consultations, 1.8 million hospitalizations, and 3100 deaths.[8] An estimated $6 billion each year is spent on medical care and lost productivity due to foodborne diseases in the U.S., most of which cause diarrhea.[8]

Acute diarrhea is defined as the passage of loose or watery stools at least 3 times in a 24-hour period for 14 days or less.[8] Most cases of acute diarrhea in adults are infectious due to viruses, bacteria, or protozoa. Consumption of tainted food, exposure to certain animals (e.g., poultry, turtles, or reptiles), exposure to children with diarrhea (e.g., day care providers), or travel to resource-limited countries can result in infection with microbes that cause diarrhea.[8] Protracted infections caused by parasites or recurrent infections due to *Clostridium difficile* may present as persistent diarrhea that lasts greater than 2 weeks.[9] In children, the causes of acute diarrhea can be related to feeding, associated with antibiotic therapy, or due to enteric viruses.[8] Chronic diarrhea is defined as the production of loose stools with or without increased stool frequency for more than 4 weeks.[10] Chronic diarrhea is rarely caused by infectious organisms.[9] Stools that are watery, bloody or fatty require individualized diagnostic testing to differentiate between infectious diarrhea, irritable bowel syndrome (IBS), small bowel dysfunction, celiac disease, malabsorption, lactase deficiency, neoplasm, pancreatic insufficiency or laxative abuse.[11]

The epidemiology of diarrhea varies by geographic region. Developing countries with limited infrastructure have more cases of pediatric infectious diarrhea caused by *Giardia*, *Campylobacter*, *Rotavirus*, and *Cryptosporidium* due to poor sanitation practices.[9] If diarrhea is not managed in children, it can lead to severe dehydration and death. It is estimated that diarrheal illnesses are responsible for 2 to 4 million childhood deaths worldwide each year.[12] Resource-rich countries, such as the U.S., tend to have more cases of acute diarrhea caused by foodborne pathogens (e.g. *Salmonella*, *Shigella*, *Escherichia coli*).[9] In resource-rich countries, older persons have increased risk of mortality associated with chronic diarrhea.[13] If untreated, chronic diarrhea may lead to dehydration and renal failure in this population.[13]

Infectious diarrhea or colitis associated with enteric infections (e.g., food poisoning) are funded conditions under the Oregon Health Plan (OHP) on line 150 of List of Prioritized Services.[14] Disorders of stomach function and other functional digestive disorders (line 531) are not funded by OHP.[14] A complete list of ICD-10 codes associated with diarrhea and their respective OHP funding lines are included in **Table 5** of **Appendix 1**. Most categories of diarrheal illness are not funded by OHP.

This class review will focus on antidiarrheal treatment in industrialized countries such as the U.S. Depending on the etiology, management of diarrhea includes oral rehydration, electrolyte replacement, diet modification, selective antimicrobial therapy or anti-diarrheal therapy.[10] Antidiarrheal therapy is used to manage diarrhea in appropriate circumstances to reduce stool frequency and abdominal pain.[15] Antimotility agents such as loperamide, diphenoxylate/atropine, opium tincture and paregoric increase intestinal transit time and enhance the potential for reabsorption of fluid and electrolytes.[15] The indications and dosing of these

agents are outlined in **Table 1**. Bismuth salicylate is an OTC antisecretory agent aimed at reducing water and electrolyte loss secondary to prolonged diarrhea.[15] It is hydrolyzed to salicylic acid in the stomach, which helps to reduce intestinal inflammation.[16] Bismuth subsalicylate has some limitations including: frequency of administration (every 30-60 minutes, up to 8 tablets per day), delayed onset of action (up to 4 hours), interaction with the absorption of other medications such as doxycyline, and has some unpleasant adverse effects (black stool, black tongue).[15] The mechanism of action and pharmacokinetics of antidiarrheal agents are outlined in **Table 3** of **Appendix 1**.

Although opium tincture has been available for many years, it has not been reviewed by the FDA to be safe and effective.[2] The original Federal Food and Drugs Act of 1906 brought drug regulation under federal law. That Act prohibited the sale of adulterated or misbranded drugs, but did not require that drugs be approved by FDA. In 1938, Congress required that new drugs be approved for safety. In 1962, Congress amended the 1938 law to require manufacturers to show that their drug products were effective, as well as safe. As a result, all drugs approved between 1938 and 1962 had to be reviewed again for effectiveness.[17] The Drug Efficacy Study Implementation (DESI) was the process used by the FDA to evaluate effectiveness in this group of drugs.[18] For a variety of historical reasons, some drugs, mostly older products including opium tincture, continue to be marketed in the U.S. without required FDA approval.[19]

The safety and efficacy of loperamide in managing acute and chronic diarrhea at therapeutic doses has been well documented since it was first marketed in the U.S. in 1977.[20] Loperamide is an opioid agonist with relatively low gastrointestinal absorption and poor blood-brain penetration.[3] Two open label studies compared the efficacy of loperamide to bismuth subsalicylate in reducing frequency of diarrhea within 24 hours.[16, 21] The details of the two studies are summarized in **Table 2**. The first study compared loperamide 4 mg for one dose followed by 2 mg after each loose stool (max 16 mg per day) to bismuth subsalicylate 30 ml every 30 minutes for 3.5 hours over 2 days in 217 subjects.[21] Students visiting seven countries in Latin America that experienced acute, nondsyenteric traveler's diarrhea were enrolled in the study. The number of unformed stools passed per treatment period (24 vs 48 hours) was used to compare the two medications. The authors found the subjects receiving loperamide passed fewer stools compared to bismuth subsalicylate during the first 24 hours of therapy ($p < 0.002$).[21] During the next 48 hours, the loperamide group passed fewer unformed stools than bismuth ($p < 0.05$).[21] Both medications were well tolerated, although constipation was experienced by more subjects in the loperamide group compared to the bismuth group ($p < 0.25$).[21] A similar study compared loperamide 8 mg per 24 hours to bismuth subsalicylate 4.9 grams over 2 days in 203 adult students traveling to Mexico who were diagnosed as having acute, non-specific diarrhea.[16] Within the first 24 hours, the number of unformed stools decreased more in the loperamide group (n= 0.4) compared with the bismuth group (n = 0.08; p = 0.01).[16] By 48 hours the decrease in unformed stools was the same for both groups (n= 0.02, p = 0.92). However, the mean time to last unformed stool was significantly decreased with loperamide (9.9 hours) compared to bismuth subsalicylate (17.3 hours; $p < 0.004$).[16] Both treatments were well tolerated and none of the adverse effects reported resulted in discontinuation of therapy.[16] Antimotility agents are not recommended for use in infectious diarrhea without antibiotic therapy.[15] In addition, these agents should not be used as monotherapy in diarrhea accompanied by bloody stool, fever or abdominal pain.[8, 15] However, bismuth is a safe alternative to loperamide in patients with fever and inflammatory diarrhea.[15]

Diphenoxylate/atropine is approved for adults and children over the age of 2 years to reduce symptoms associated with diarrhea.[22] Atropine is added to this combination therapy to decrease abuse of diphenoxylate, which is a meperidine analog.[23] Diphenoxylate/atropine should not be used in patients with diarrhea due pseudomembranous enterocolitis or due to enterotoxin producing bacteria such as: *Shigella, Salmonella,* toxigenic *E.Coli*, *Campylobacter jejuni* or *C.difficile*.[22] There are no comparative trials of diphenoxylate/atropine with other antidiarrheal agents.

Noninfectious diarrhea in HIV-infected patients is usually secretory and caused by anti-retroviral therapy, HIV-associated enteropathy or HIV-associated malignancies, or pancreatitis.[24] All classes of anti-retrovirals can cause diarrhea; however, ritonavir-boosted protease regimens are particularly associated with diarrhea.[24] A clinical trial review indicated up to 19% of anti-retroviral treated patients experienced drug-related diarrhea that was least moderate in intensity.[25]

Most anti-diarrheal agents do not have targeted activity against the cause of secretory diarrhea and are not very effective.[24] Crofelemer inhibits intestinal luminal chloride channels, which reduces the efflux of sodium and water into the gastrointestinal (GI) lumen.[24] Crofelemer is poorly absorbed from the GI tract so systemic exposure is minimal.[24] A phase 3, randomized double-blind trial conducted in HIV-seropositive patients on anti-retroviral treatment evaluated the optimal dose, efficacy and safety of crofelemer for noninfectious diarrhea.[5] The details of this study are summarized in **Table 2**. Patients were stabilized on an anti-retroviral regimen for ≥ 4 weeks with a history of diarrhea for ≥ 1 month. This study was completed in 2 stages. The first stage randomized 196 patients with chronic diarrhea to 3 doses of crofelemer (125mg, 250mg, or 500mg) or placebo twice daily over 4 weeks. The second stage was completed in 180 new patients to compare crofelemer 125mg orally twice daily to placebo over 4 weeks. Primary efficacy analysis was the percentage of patients who achieved clinical response (2 or less watery stools per week during ≥ 2 of 4 weeks).[5] More patients receiving crofelemer 125 mg twice daily achieved clinical response versus placebo (17.6% vs 8 % p = 0.01).[5] Based on this data, the number of patients needed to treat to achieve one patient with clinical response is 10 patients. Crofelemer 125 mg twice daily resulted in a greater change from baseline in number of daily watery bowel movements (p= 0.04) and daily consistency score (p = 0.02) versus placebo.[5] Crofelemer was minimally absorbed and well tolerated with a safety profile comparable to placebo.[5] The authors concluded crofelemer provided significant improvement in diarrhea symptoms in HIV-seropositive patients taking stable anti-retroviral therapy.[5] Crofelemer has been studied in other diarrheal conditions including IBS-associated diarrhea, traveler's diarrhea, and acute infectious diarrhea and has not been found to be very effective in treating these conditions.[24] However, it is only approved by the FDA for management of diarrhea specifically associated with anti-retroviral therapy in HIV-seropositive individuals.[26] There are no head-to-head trials comparing crofelemer to other anti-diarrheal agents.

The use of antimotility agents in children less than 5 years of age has been discouraged by the WHO due to safety concerns.[27] Bismuth subsalicylate, loperamide diphenoxylate/atropine, and paregoric are the only antidiarrheal agents that are FDA approved for use in children over 2 years of age. For children under the age of 13 years, the liquid formulation of diphenoxylate/atropine is preferred to enhance appropriate dosing.[23] Pediatric dosing recommendations for antidiarrheal agents are outlined in **Table 1**.

A recent study evaluated loperamide exposures reported to the National Poison Data System to assess trends in loperamide toxicity associated with intentional misuse and abuse.[28] There was a 91% increase in reported loperamide exposures from 2010 to 2015, of which half were single-agent loperamide use only.[28] Loperamide exposures reported to the National Poison Data System increased at approximately 38 cases per year (95% confidence interval (CI) 32.5 to 42.9; $P < 0.0001$).[28] Fifteen deaths were reported during this time frame, of which 8 involved single-agent loperamide abuse.[28] The FDA issued a warning in June 2016 that higher than recommended doses of loperamide, including through abuse or misuse of the product, can cause serious cardiac events that can lead to death.[3] Forty eight cases of serious cardiac events associated with loperamide use have been reported to the FDA since 1976.[3] Thirty one of the cases resulted in hospitalizations and 10 patients died.[3] The most frequently reported cardiac events were syncope (n=24), cardiac arrest (n=13), QT interval prolongation (n=13), ventricular tachycardia (n=10), and Torsades de Pointes (n=7).[3] The risk of these cardiac events, including abnormal heart rhythms, was increased when high doses of loperamide were taken with other medications that interact with loperamide.[3] Drugs that interact with loperamide include: cimetidine, clarithromycin, erythromycin, gemfibrozil, itraconazole, ketoconazole, quinidine, ranitidine and ritonavir. The majority of reported cardiac events occurred in individuals intentionally misusing and abusing high doses of loperamide in attempts to self-treat opioid withdrawal symptoms or to achieve a feeling of euphoria.[3] In cases of abuse, patients have often combined loperamide with other drugs that inhibit its metabolism or increase its absorption in order to enhance the euphoric effects of loperamide.[3]

The FDA issued warning in March 2016 about safety issues associated with the entire class of opioid medications including diphenoxylate/atropine and paregoric.[4] These risks include: potentially harmful interactions with numerous other medications, leading to serotonin syndrome; problems in which the adrenal glands do not produce adequate amounts of cortisol; and decreased sex hormone levels, possibly leading to reduced interest in sex, impotence, or

infertility.[4] The FDA is requiring class-wide safety labeling changes for all opioid pain medications warning of these risks.[4] A summary of warnings and precautions for all antidiarrheal agents is outlined in **Table 4** of **Appendix 1**.

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.[23]

Antidiarrheal Drug	**Indication(s)**	**Strength** (all routes oral)	**Pediatric Dose/Frequency**	**Adult Dose/Frequency**
Loperamide (Imodium®)	• Acute diarrhea • Chronic diarrhea • Traveler's diarrhea • High output ileostomy	2 mg tablet 2 mg capsule 1 mg/7.5 mL suspension	Age: 2-5 years (13-20 kg): 1 mg TID Age: 6-8 years (20-30 kg): 2 mg BID Age: 8-11 years (>30 kg): 2 mg TID Age ≥12 years: see adult dosing	Age ≥ 12 years: 4 mg followed by 2 mg after each loose stool (max 16 mg/day)
Bismuth-subsalicylate (Pepto-Bismol®)	• Diarrhea • *H. pylori* infection	525 mg/15 mL suspension 262 mg tablet	Age <12 years: not recommended	524 mg every 0.5 to 1 hour PRN (max 8 doses or 4192 mg per day) *H. pylori* dosing is 525 mg po QID for 10-14 days as part of a multi-drug regimen
Diphenoxylate/Atropine (Lomotil®)	• Diarrhea	2.5 mg/0.025 mg/5 mL solution 2.5 mg/0.025 mg tablet	Age: ≥2 years: 0.3-0.4 mg/kg/day *oral solution* divided QID (max 20 mg diphenoxylate per day)	2 tablets or 10 mL solution QID until control achieved (max 20 mg of diphenoxylate per day (40 mL or 8 tablets)
Opium Tincture	• Diarrhea	10 mg/mL tincture	Safety and efficacy not established in children	6 mg QID
Paregoric	• Diarrhea	2 mg/5 mL solution	0.1 – 0.2 mg/kg daily to QID	5 -10 mL daily to QID
Crofelemer (Mytesi®)	• Non-infectious diarrhea in HIV+ adults on stable antiretroviral therapy	125 mg delayed-release tablets	Safety and effectiveness not established	125 mg BID

Abbreviations: BID = twice daily; kg = kilograms; mg = milligrams; mL = milliliters; PRN = as needed; QID = four times daily

Table 2. Summary of Pivotal Studies Completed.

<table>
<tr><th>Study</th><th>Comparison</th><th>Population</th><th>Primary Outcome</th><th>Results</th></tr>
<tr>
<td>Johnson PC et al[21]

OL RCT</td>
<td>Loperamide 4 mg followed by 2 mg after each stool (max 16 mg per day) over 2 days

Vs.

Bismuth Subsalicylate 30 mL every 30 min for 3.5 hours over 2 days (7 doses or 210 mL total)</td>
<td>Students visiting 7 Latin American countries

Treatment of acute nondsyenteric traveler’s diarrhea

N = 217</td>
<td>Improvement (decrease in diarrhea severity) defined as: decrease by half of the number of unformed stools compared to the previous 24 hours

Or

Disappearance (total relief) of diarrhea</td>
<td>Percent with Improvement and Relief in Diarrhea within 24 hours

Loperamide 72/111 (64%)

Bismuth 45/107 (42%)

Loperamide favored over bismuth (p<0.03 for relief and p<0.0001 for improvement)</td>
</tr>
<tr>
<td>DuPont HL et al[16]

OL PG RCT</td>
<td>Loperamide 4 mg followed by 2 mg after each unformed stool (max 8 mg per day)

Vs.

Bismuth 612.5 mg (35 mL) every 30 minutes as needed up to 4.9 grams per 24 hours (8 doses maximum)</td>
<td>Adult students from US or Latin America with acute diarrhea

N = 203</td>
<td>Number of unformed stools passed

And

Time elapsed from start of therapy to occurrence of last unformed stool</td>
<td>Average Number of Unformed Stools per 12 hour period after initiation of therapy
<table>
<tr><th>Period</th><th>Loperamide</th><th>Bismuth Salicylate</th><th>p-value*</th></tr>
<tr><td>1 – 12 hours</td><td>0.9</td><td>2.3</td><td>0.0001</td></tr>
<tr><td>2 – 24 hours</td><td>0.4</td><td>0.8</td><td>0.01</td></tr>
<tr><td>3 – 36 hours</td><td>0.3</td><td>0.6</td><td>0.17</td></tr>
<tr><td>4 – 48 hours</td><td>0.2</td><td>0.2</td><td>0.92</td></tr>
</table>
Time to last unformed stool (mean time)
Loperamide: 9.9 hours
Bismuth subsalicylate: 17.3 hours
p<0.004</td>
</tr>
<tr>
<td>Macarthur RD et al[5]

PC DB RCT
Phase 3

4 weeks</td>
<td><u>Stage 1:</u>
Crofelemer 125 mg, 250 mg, or 500 mg po BID
Vs.
Placebo

<u>Stage 2:</u>
Crofelemer 125 mg po BID
Vs.
Placebo</td>
<td>HIV sero-positive patients with chronic diarrhea (≥ 1 month) on antiretroviral therapy ≥ 1 month

Stage 1 (dose finding 125mg, 250mg, or 500mg BID)
N = 196

Stage 2: (crofelemer 125mg BID vs placebo)
N = 180</td>
<td>Percent of patents who achieved clinical response (decrease in watery stools).</td>
<td>Stage 2 results: Patients with clinical response (defined as ≤ 2 watery stools per week during ≥2 of 4 weeks)
<table>
<tr><th>Crofelemer 125 mg po BID (n=136)</th><th>Placebo (n=138)</th><th>Treatment Difference</th><th>p-value</th></tr>
<tr><td>24/136 (17.6%)</td><td>11/138 (8.0%)</td><td>9.6%</td><td>0.0096</td></tr>
</table>
</td>
</tr>
</table>

Abbreviations: BID = twice daily; OL = open label; PC = placebo-controlled; PG = parallel group; po = orally; RCT = randomized controlled trial

Methods:
A Medline literature search for 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), Cochrane Collection, 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.

Conducting clinical trials for the treatment of diarrhea is difficult due to the different causes of diarrhea, varying definitions of diarrhea based on frequency and duration of unformed stools, and different patient populations(from children to the elderly).[20] Consequently, there is insufficient evidence to guide the use of antidiarrheal agents as there are very few head-to-head trials. However, 2 systematic reviews were identified and assessed for this review.

Systematic Reviews:
Adjunctive Loperamide with Antibiotics for Traveler's Diarrhea
A Cochrane Collaboration review established an effective advantage of antibiotic therapy, compared with placebo, for treatment of traveler's diarrhea.[29] This systematic review evaluated the effect of loperamide in conjunction with antibiotic therapy in adults on treatment outcomes.[1] Clinical trials that studied treatment of adults with infectious traveler's diarrhea in which an adjunctive antimotility agent was used were eligible to be included in the review. Nine studies published during 1990-2007 consisting of 12 different antibiotic regimens with adjunctive loperamide met inclusion criteria to be included for analysis.[1] The average size of the treatment arms was 60 patients; the smallest involved 43 patients, the largest involved 106 patients, and all were randomized, double-blind, placebo-controlled trials, except 2, which were randomized, evaluator-blind clinical trials.[1] Six studies evaluated U.S. student travelers to Mexico. The other 3 studies included U.S. military personnel in Egypt, Thailand, and Turkey. The mean age of the study populations was 24 years (9 studies; age range, 23–27 years), and patients presented a mean of 36 h (n=7 studies; range, 23–48 h) after symptom onset, with a median of 6 stools in the previous 24 h (n=7 studies; range, 2.3–7).[1] The authors found the studies to be of moderate quality.[1] Among 6 paired studies comparing antibiotics alone versus antibiotics in combination with loperamide, the odds of clinical cure at 24 hours and 48 hours favored combination therapy (odds ratios [OR] 2.6 (95% CI, 1.8-3.6) and OR 2.2 (95% CI, 1.5-3.1), respectively).[1]. Most of the studies independently demonstrated that combination regimens offer an advantage of antibiotic alone regimens for clinical cure at the first 24–48 h. By 72 hours, the addition of loperamide did not appear to offer any significant advantage to antibiotic treatment alone.[1] Time to last unformed stool (TLUS) after initiation of therapy was also evaluated. Five of 6 studies had extractable information on this outcome; although all demonstrated negative mean TLUS durations (meaning that adjunctive therapy decreased the time after treatment to last diarrheal stool, compared with antibiotics treatment alone) of 2–23 h, there was considerable heterogeneity among the studies (P<.001)[1] When estimates of TLUS among studies with evaluable loperamide antibiotic combination regimens were pooled (10 studies) using a random-effects model, it was estimated that TLUS for these combination treatment regimens was 17 h (95% CI, 9–24 h).[1] The most common adverse effect of loperamide was constipation, which was rarely reported.[1] There was moderate evidence that antibiotic therapy with adjunctive loperamide offers an advantage over antibiotics alone by decreasing the duration of illness and increasing the probability of early clinical cure in adult patients with travelers' diarrhea.[1]

Loperamide in Children

A systematic review and meta-analysis was conducted in children to evaluate the safety and efficacy of loperamide compared to placebo.[6] Thirteen studies met inclusion criteria established by the reviewers. Four study design aspects were evaluated: allocation of concealment, generation of allocation sequence, blinding and inclusion of all randomized participants. The authors categorized the 4 study design characteristics as adequate, not adequate or unclear. Most of the studies did not meet the requirements for adequate methodological quality and only 4 studies provided outcome data that could be combined.[6] The primary outcomes of interest were the characteristics of the clinical course of diarrhea and the incidence of adverse effects. [6] Compared with patients who received placebo, patients allocated to loperamide were less likely to continue to have diarrhea at 24 hours (prevalence ratio 0.66, 95% CI: 0.57 to 0.78), had a shorter duration of diarrhea by 0.8 days (95% CI: 0.7 to 0.9 days), and had a lower count of stools at 24 hours (0.84, 95% CI: 0.77 to 0.92).[6] Serious adverse events, defined as ileus, lethargy, or death, were reported in eight out of 927 children allocated to loperamide (0.9%, 95% CI: 0.4% to 1.7%).[6] Serious adverse events were not reported in any of the 764 children allocated to placebo (0%, 95% CI: 0% to 0.5%).[6] Low quality evidence shows that loperamide appears to decrease diarrhea duration and frequency in children when used as an adjunct to oral or intravenous hydration.[6] Limitations of this systematic review included a lack of consistency in outcome measures and very few well designed studies that could be included in the meta-analysis.

References:

1. Riddle MS, Arnold S, and Tribble DR. Effect of adjunctive loperamide in combination with antibiotics on treatment outcomes in traveler ’s diarrhea: a systematic review and meta-analysis. *Clin Infect Dis*. 2008;47(8):1007-1014. doi:10.1086/591703.

2. DailyMed - OPIUM TINCTURE DEODORIZED- morphine tincture solution. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=674a969a-707d-41a9-b7c3-b90cbf2909e3. Accessed December 1, 2016.

3. Research C for DE and. Drug Safety and Availability - FDA Drug Safety Communication: FDA warns about serious heart problems with high doses of the antidiarrheal medicine loperamide (Imodium), including from abuse and misuse. http://www.fda.gov/Drugs/DrugSafety/ucm504617.htm. Accessed December 5, 2016.

4. Commissioner O of the. Safety Alerts for Human Medical Products - Opioid Pain Medicines: Drug Safety Communication - New Safety Warnings Added to Prescription Opioid Medications. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm491715.htm. Accessed December 5, 2016.

5. Macarthur RD, Hawkins TN, Brown SJ, et al. Efficacy and safety of crofelemer for noninfectious diarrhea in HIV-seropositive individuals (ADVENT trial): a randomized, double-blind, placebo-controlled, two-stage study. *HIV Clin Trials*. 2013;14(6):261-273. doi:10.1310/hct1406-261.

6. Li S-TT, Grossman DC, Cummings P. Loperamide therapy for acute diarrhea in children: systematic review and meta-analysis. *PLoS Medicine / Public Library of Science*. 2007;4(3).

7. Farthing M, Salam MA, Lindberg G, et al. Acute diarrhea in adults and children: a global perspective. *J Clin Gastroenterol*. 2013;47(1):12-20. doi:10.1097/MCG.0b013e31826df662.

8. Guerrant RL, Van Gilder T, Steiner TS, et al. Practice guidelines for the management of infectious diarrhea. *Clin Infect Dis*. 2001;32(3):331-351. doi:10.1086/318514.

9. DuPont HL. Persistent Diarrhea: A Clinical Review. *JAMA*. 2016;315(24):2712-2723. doi:10.1001/jama.2016.7833.

10. American Gastroenterological Association medical position statement: guidelines for the evaluation and management of chronic diarrhea. *Gastroenterology*. 1999;116(6):1461-1463.

11. Fine KD, Schiller LR. AGA technical review on the evaluation and management of chronic diarrhea. *Gastroenterology*. 1999;116(6):1464-1486.

12. Zella GC, Israel EJ. Chronic diarrhea in children. *Pediatr Rev*. 2012;33(5):207-217-218. doi:10.1542/pir.33-5-207.

13. Clinical Evidence Handbook: Diarrhea in Adults (Acute) - American Family Physician. http://www.aafp.org/afp/2008/0815/p503.html. Accessed November 29, 2016.

14. Health Evidence Review Commission Prioritized List of health services. https://www.oregon.gov/oha/herc/Pages/PrioritizedList.aspx. Accessed December 1, 2016.

15. Casburn-Jones AC, Farthing MJG. Management of infectious diarrhoea. *Gut*. 2004;53(2):296-305.

16. DuPont HL, Flores Sanchez J, Ericsson CD, et al. Comparative efficacy of loperamide hydrochloride and bismuth subsalicylate in the management of acute diarrhea. *Am J Med*. 1990;88(6A):15S-19S.

17. Research C for DE and. FDA Basics - What are unapproved drugs and why are they on the market? http://www.fda.gov/AboutFDA/Transparency/Basics/ucm213030.htm. Accessed December 12, 2016.

18. Marketed Unapproved Drugs – Compliance Policy Guide - ucm070290.pdf. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070290.pdf. Accessed December 12, 2016.

19. Research C for DE and. Unapproved Prescription Drugs: Drugs Marketed in the United States That Do Not Have Required FDA Approval. http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/enforcementactivitiesbyfda/selectedenforcementactionsonunapproveddrugs/default.htm. Accessed December 12, 2016.

20. Ericsson CD, Johnson PC. Safety and efficacy of loperamide. *Am J Med*. 1990;88(6A):10S-14S.

21. Johnson PC, Ericsson CD, DuPont HL, Morgan DR, Bitsura JA, Wood LV. Comparison of loperamide with bismuth subsalicylate for the treatment of acute travelers' diarrhea. *JAMA*. 1986;255(6):757-760.

22. Prescribing Information: Lomotil (Diphenoxylate/atropine) NY, NY,Pfizer, Inc. October 2005. https://www.pfizer.com/files/products/uspi_lomotil.pdf. Accessed December 12, 2016.

23. MICROMEDEX® [online database]. 2016. United States: Truven Health Analytics; Accessed November 1, 2016. http://www.micromedexsolutions.com.

24. Chordia P, MacArthur RD. Crofelemer, a novel agent for treatment of non-infectious diarrhea in HIV-infected persons. *Expert Rev Gastroenterol Hepatol*. 2013;7(7):591-600. doi:10.1586/17474124.2013.832493.

25. Hill A, Balkin A. Risk factors for gastrointestinal adverse events in HIV treated and untreated patients. *AIDS Rev*. 2009;11(1):30-38.

26. Mytesi - crofelemer 125mg (Prescribing Information). Napo Pharmaceuticals. San Francisco, CA. June 2016. http://www.mytesi.com/. Accessed December 7, 2016.

27. THE TREATMENT OF DIARRHOEA A manual for physicians and health care workers. World Health Care Organization v05 1 final.doc - 9241593180.pdf. http://apps.who.int/iris/bitstream/10665/43209/1/9241593180.pdf. Accessed December 5, 2016.

28. Vakkalanka JP, Charlton NP, Holstege CP. Epidemiologic Trends in Loperamide Abuse and Misuse. *Ann Emerg Med*. November 2016. doi:10.1016/j.annemergmed.2016.08.444.

29. De Bruyn G, Hahn S, Borwick A. Antibiotic treatment for travellers' diarrhoea. *Cochrane Database Syst Rev*. 2000;(3):CD002242. doi:10.1002/14651858.CD002242.

30. Lexicomp Online. (Internet Database). Hudson, OH: Wolters Kluwer, Inc. Updated June 2016.Accessed December 1, 2016.

Appendix 1: Specific Drug Information

Table 3. Clinical Pharmacology and Pharmacokinetics.[23,30]

Drug Name	Mechanism of Action	Absorption	Metabolism/Excretion	Pharmacokinetics
Loperamide (Imodium®)	Inhibit peristalsis Antisecretory	Bioavailability 0.3% (poor)	Renal Excretion 1% Fecal Excretion 25-40%	Half-life: 7-15 hours
Bismuth-subsalicylate (Pepto-Bismol®)	Undetermined	Bismuth subsalicylate: Hydrolyzed in GI tract to bismuth and salicylic acid Bismuth: <1% absorbed from GI tract into systemic circulation Salicylic acid: >80% absorbed following oral administration	Salicylic acid: Extensively metabolized Bismuth: Excreted principally via urine and biliary routes. Salicylic acid: About 10% excreted unchanged in urine	Half-life: 5-11 days Cmax: 40 mcg/L (tablet) Vd: 170 mL/kg (salicylic acid)
Diphenoxylate/Atropine (Lomotil®)	Slows intestinal motility (diphenoxylate) *Sub-therapeutic doses of atropine are added to discourage abuse	Bioavailability >90% (good)	Metabolism: Hepatic to active metabolite: diphenoxylic acid Excretion: Renal 14%; fecal: 49%	Half-life: 2.5 hours (diphenoxylate) Cmax: 163 mg/mL Vd: 324 L
Opium Tincture	Slows intestinal motility	Variable	Hepatic: Conjugation Renal: 75%	N/A
Paregoric	Slows intestinal motility	Variable	Hepatic: Conjugation Renal: 75%	N/A
Crofelemer (Mytesi®)	Inhibits chloride ion channels that regulate chloride ion and fluid secretion by intestinal epithelial cells, resulting in blockade of chloride ion secretion and the associate water loss associated with diarrhea	Minimal	No metabolites have been identified Elimination route has not been identified in humans due to minimal systemic absorption	N/A

Abbreviations: Cmax = maximal concentration in blood; GI = gastrointestinal; Vd = volume of distribution

Use in Specific Populations:
Loperamide: Loperamide is contraindicated in pediatric patients <2 years of age.[30]

Bismuth subsalicylate: Do not use bismuth subsalicylate in children or adolescents who have or are recovering from varicella or influenza-like symptoms.[30] Changes in behavior accompanied by nausea and vomiting in children or adolescents taking the drug may be an early sign of Reye's syndrome.[30]

Diphenoxylate/atropine: Use with caution in children; not recommended for use in children <2 years of age.[30] Younger children may be predisposed to delayed toxicity; signs of atropinism may occur even at recommended doses, especially in patients with Down syndrome.[30]

Opium tincture: Not recommended for use in children.[2]

Drug Safety: Black Boxed Warnings:
Loperamide: Cases of torsades de pointes, cardiac arrest, and death have been reported with the use of a higher than recommended dosage of loperamide. [30] Avoid dosages higher than recommended in adults and pediatric patients ≥2 years due to the risk of serious cardiac adverse reactions.[30]

Opium Tincture/Paregoric: Potential for error: Do not confuse paregoric with opium tincture which is 25-times more potent.[30]

Table 4. Summary of Warnings and Precautions.[30]

Warning/Precaution	Loperamide	Bismuth	Diphenoxylate/Atropine	Opium Tincture	Paregoric	Crofelemer
CNS Effects (Drowsiness/Dizziness)	X		x	X	X	
Constipation	X					
Cardiac Arrest	X					
Reye's Syndrome		X				
Tongue Discoloration		X				
Use with Caution in Hepatic Impairment			X	X	X	
Uses with Caution in Renal Impairment			X		X	
Hypotension				X	X	
Flatulence/Nausea						X

Table 5. ICD-10 Codes Associated with Diarrhea and Associated OHP Funding.[14]

Diagnosis	ICD-10 Code	OHP Funding Line	Funding Status
Enteric Infection/Food Poisoning	A09	150	Funded
Non-infective gastroenteritis and colitis	K52.9	555	Not Funded
Irritable bowel syndrome with diarrhea	K58.0	531	Not Funded
Functional diarrhea	K59.1	531	Not Funded
Non-infective neonatal diarrhea	P78.3	531	Not Funded

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1946 to November Week 4 2016

1. Bismuth subsalicylate.mp 505
2. exp Diphenoxylate/ 364
3. lomotil.mp. 105
4. exp Loperamide/ 1550
5. exp Opium/ 2918
6. paregoric.mp. 54
7. crofelemer.mp 23
8. 1 or 2 or 3 or 4 or 5 or 6 52332
9. limit 7 to (full text and humans and (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta-analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 107
10. diarrhea {No Related Terms} 87681
11. 8 and 9 101

Drug Use Research & Management Program
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Class Review: Vitamin D Analogs

Date of Review: January 2017

Purpose for Class Review:
Oral and intravenous (IV) vitamin D analogs are important treatment options for secondary hyperparathyroidism and low levels of vitamin D associated with chronic kidney disease (CKD). Evidence on effectiveness and harms will be reviewed to make recommendations to the Oregon Health Authority (OHA) on criteria for use.

Research Questions:
1. In children and adult patients with CKD, what is the evidence for differences in efficacy or effectiveness (i.e., parathyroid hormone changes, mortality, cardiovascular outcomes, need for renal replacement therapy) between vitamin D analogs used for the treatment of secondary hyperparathyroidism?
2. In children and adult patients with CKD, what is the evidence for differences in harms (i.e., hypercalcemia, hyperphosphatemia) between drug therapies used for the treatment of secondary hyperparathyroidism?
3. Are there subpopulations (i.e., different stages of chronic kidney disease, dialysis requirements, socioeconomic status, age, race, ethnicities) in which one vitamin D analog may be more effective or associated with less harm than other vitamin D analog for the treatment of secondary hyperparathyroidism?

Conclusions:
- The evidence review on vitamin D analogs found 4 systematic reviews and meta-analyses, 3 randomized-controlled trials and 3 clinical practice guidelines from the U.S. Department of Veterans Affairs/Department of Defense (VA/DoD), National Institute for Health and Care Excellence (NICE), and Kidney Disease Improving Global Outcomes (KDIGO) recommendations for patients with CKD.[1-10] The evidence for vitamin D analogs is limited due to lack of long-term data on clinically meaningful outcomes such as mortality, bone fracture rates, and cardiovascular outcomes. Surrogate endpoints such parathyroid hormone (PTH) levels are subject to large variations between assays which make comparisons between clinical trials difficult. Some results analyzed vitamin D analogs as either established agents (vitamin D, 24,25 hydroxyvitamin D3, 1,25 dihydroxyvitamin D3 [calcitriol] and 1α-hydroxyvitamin D3 [alfacalcidol]) or newer vitamin D compounds (doxercalciferol, paricalcitol, falecalcitriol and maxacalcitol). Afacalcidol, maxacalcitol and falecalcitriol are not available in the United States (US).
- Evidence for use of vitamin D analogs in children with CKD on growth rate, bone fracture rates, electrolyte changes and cardiovascular disease is insufficient.[3]
- Evidence for use of vitamin D analogs in adults with CKD to impact fracture rates, bone pain, parathyroidectomy, cardiovascular outcomes, and need for renal replacement therapy is insufficient. Comparative efficacy between the treatments is also insufficient.

- Low quality evidence from small, short-term studies suggest there is no mortality benefit for vitamin D analogs in patients with stage 2-4 CKD (RR 1.40; 95% CI, 0.38 to 5.15).[1] Mortality compared to placebo was not different for established vitamin D analogs (RR 1.49; 95% CI, 0.14 to 15.69) compared to newer vitamin D analogs (RR 1.09; 95% CI, 0.16 to 7.34). In patients on hemodialysis, no difference was observed between patients who received vitamin D analogs or placebo (117 deaths vs. 116 deaths, respectively (p=0.67) (based on low quality of evidence).[2]
- There is moderate quality evidence, based on 2 trials, that newer vitamin D analogs decrease PTH levels more than 30% from baseline in 87.5% of patients compared to 11% of patients on placebo who have CKD not requiring dialysis (RR 7.87; 95% CI 4.87 to 12.73).[1] There was insufficient evidence to compare this surrogate outcome with older, established vitamin D analogs.
- There is moderate quality evidence in patients requiring dialysis that vitamin D analogs decrease PTH levels more than 30% in 73% of patients compared to 10% in placebo-treated patients (RR 5.90; 95% CI, 3.17 to 10.96).[2] In a separate analysis between paricalcitol and placebo in patients undergoing hemodialysis, paricalcitol was found to decrease PTH levels more than 30% from baseline in 73% of patients receiving IV paricalcitol compared to 10% of placebo-treated patients (RR 6.37; 95% CI, 4.64 to 8.74; P<0.001).[4] Low quality evidence found that in patients requiring dialysis, paricalcitol decreased PTH levels more than 30% from baseline in 61.1% of patients compared to 73.3% of calcitriol treated patients (p=0.29) based on one small randomized-controlled trial.[5]
- Extended-release (ER) calcifediol decreased PTH levels in 2 identical, double-blind, randomized, placebo-controlled, 26-week trials in patients (n= 429) with stage 3 or 4 CKD and secondary hyperparathyroidism. Low strength of evidence found ER calcifediol to reduce PTH levels by 30% or more from baseline in 33% of patients compared to 8% in the placebo group in the first study (Study A) and by 34% and 7%, respectively, in the second study (Study B) (NNT=4 for both studies).[6]
- There is low quality evidence that paricalcitol decreases proteinuria (RR 1.68; 95% CI, 1.25 to 2.25; P<0.001).[5]
- There is moderate quality evidence to not recommend routinely prescribing vitamin D analogs to patients with CKD unless there is evidence of vitamin D deficiency or PTH suppression.[7]
- Common harms associated with vitamin D analogs are disturbances in calcium and phosphate levels. Patients with CKD on dialysis and patients with CKD not on dialysis were analyzed separately. There is moderate quality evidence that use of vitamin D analogs result in a statistically significant higher incidence of hypercalcemia than placebo in patients with CKD not requiring dialysis (5.2% vs. 3.9%, respectively; p=0.022)[1] In patients requiring dialysis, established vitamin D analogs had a 31% incidence of hypercalcemia compared to 10% in placebo-treated patients (p=0.26) and newer vitamin D analogs had a 43% risk compared to 0% risk with placebo (p=0.020).[1]
- There is low quality evidence that there was not a meaningful clinical difference between vitamin D analogs and placebo in risk of hyperphosphatemia.[2]
- In comparisons in patients requiring dialysis, there was low strength of evidence of no difference for risk of hypercalcemia or hyperphosphatemia between vitamin D analogs.

Recommendations:

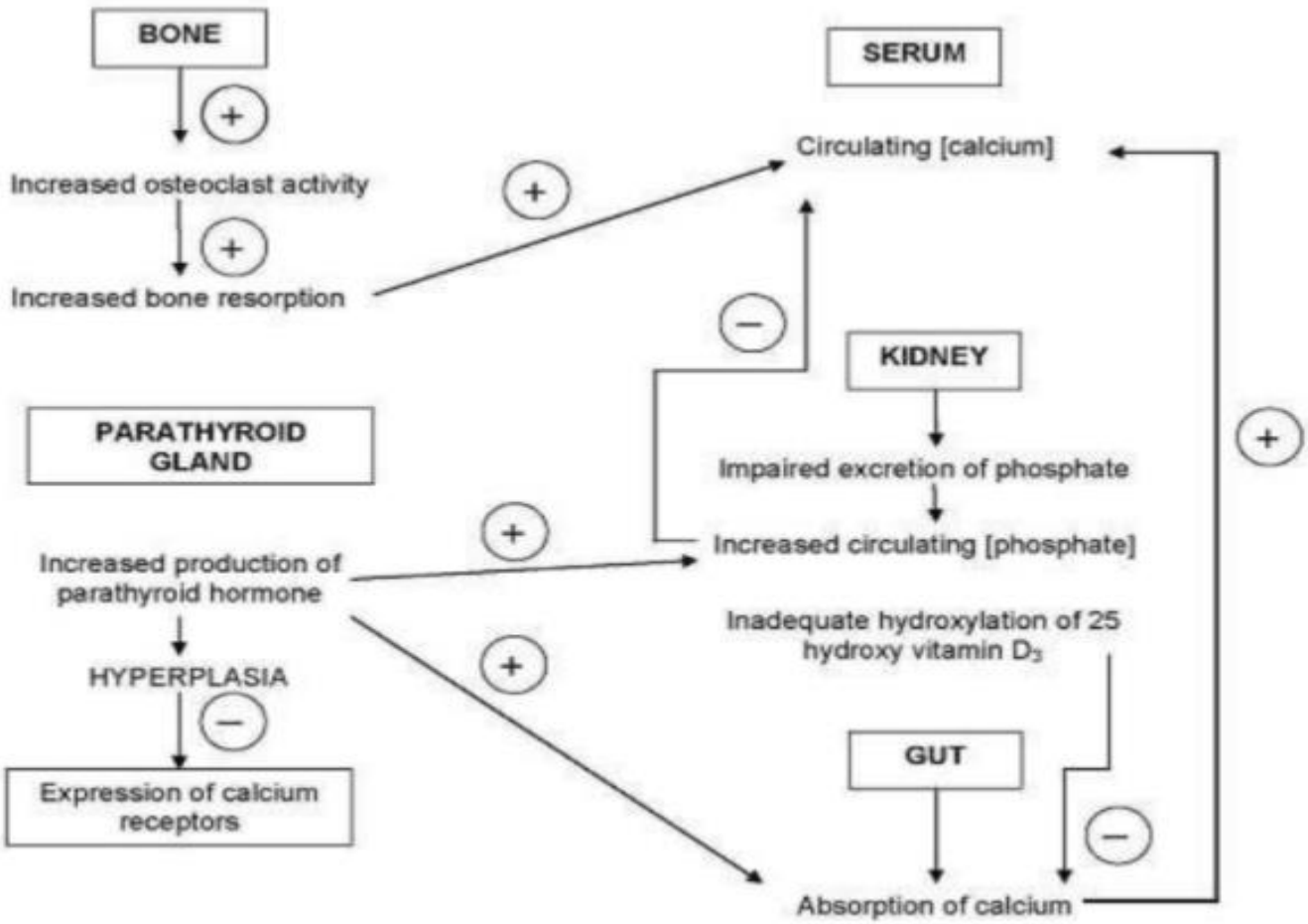
- Add a PDL class for Vitamin D analogs on the Oregon Health Plan (OHP) fee-for-service practitioner-managed prescription drug plan.
- There is no evidence to suggest that newer vitamin D analogs are more effective or associated with less harm than the preferred agent calcitriol. Recommend to continue to keep calcitriol as the only preferred vitamin D analog and designate paricalcitol, doxercalciferol and calcifediol non-preferred.

Background:

Mineral metabolism can be altered in patients with CKD (Figure 1).[1] Altered mineral metabolism can manifest as elevated phosphorous levels, low serum calcium, low vitamin D levels and increased PTH levels. Abnormalities results from reduced vitamin D formation due to insufficiency of kidney function.[1] Vitamin D is necessary for the absorption of calcium and maintenance of calcium homeostasis. Low vitamin D levels cause hypocalcemia that results in stimulation of the parathyroid gland. Abnormal stimulation of the parathyroid gland causes elevated PTH levels leading to secondary hyperparathyroidism (SHPT). Additionally, bone turnover can be accelerated to compensate for low calcium levels and result in compromised bone integrity.[8] Impaired kidney function also leads to decreased excretion of phosphate which potentiates hypocalcemia due to precipitation of phosphorous with calcium in the tissues.[1] The mineral imbalances associated with CKD are called chronic kidney disease mineral-bone disorder (CKD-MBD).[8]

Elevated calcium and phosphorous levels are associated with increased morbidity and mortality demonstrating the importance of normalizing calcium and phosphorous levels.[9] Abnormal bone turnover, tissue mineralization (calcium deposits in tissue), growth in children, arterial, valvular and myocardial calcification and other soft tissue calcification may result from hypocalcemia and hyperphosphatemia.[10] Elevated PTH levels have been linked to increased risk of mortality in patients with CKD based on observational data.[1] The National Kidney Foundation recommends supplementation with ergocalciferol and cholecalciferol to correct disturbances when there is suspected or documented vitamin D deficiency in patients with CKD.[7] When ergocalciferol or cholecalciferol fail to correct PTH levels then vitamin D analogs are initiated.[6] Vitamin D analogs suppress PTH secretion and are thought to be more selective and less likely to cause hypercalcemia and hypophosphatemia than ergocalciferol and cholecalciferol. Hypercalcemia and hyperphosphatemia limit the use and doses of vitamin D analogs because these conditions are associated with increased adverse cardiovascular events and mortality.[2,9] Contraindications to vitamin D analogs include phosphorous concentrations greater than 5.5 mg/dL and serum hypercalcemia (>9.5 mg/dL) due to their associated increase risk for metastatic and vascular calcification.[1,2]

Figure 1. Mineral metabolism in chronic kidney disease



Palmer SC, McGregor DO, Craig JC, Elder G, Macaskill P, Strippoli GF. Vitamin D compounds for people with chronic kidney disease not requiring dialysis. Cochrane Database Syst Rev. 2009;(4):CD008175 doi:10.1002/14651858.CD008175.

Four vitamin D analogs have been approved by the U.S. Food and Drug Administration (FDA): calcifediol, calcitriol, doxercalciferol, and paricalcitol (Table 1).[11–14] Studies have shown the oral and intravenous (IV) formulations of calcitriol similarly suppress PTH and result in similar adverse events. Adynamic bone disease, abnormally low bone turnover, may also occur if vitamin D analogs are used when PTH levels are less than 150 pg/mL and are therefore not recommended.

Table 1. Indications and Dosing [12-15]

Drug Name	Indication(s)	Strength/Route	Dose and Frequency
Calcitriol	- Secondary hyperparathyroidism in patients with moderate to severe CKD (CrCl 15 to 55 mL/min) not on dialysis - Hypocalcemia/metabolic bone disease in patients undergoing chronic renal dialysis - Hypocalcemia in hypoparathyroidism/pseudohypoparathyroidism	0.25 mcg or 0.5 mcg oral capsules 1 mcg/mL oral solution	Initiate at the lowest dose; titrate dose according to twice weekly serum calcium levels. Obtain serum calcium levels once monthly when on maintenance therapy. Hypocalcemia (dialysis): initiate at 0.25 mcg/day; increased by 0.25 mcg/day every 4 to 8 weeks if needed Hypocalcemia (pre-dialysis): initiate at 0.25 mcg/day; may increase to 0.5 mcg/day if needed (0.01-0.015 mcg/kg/day in pediatric patients age <3 years) Hypoparathyroidism: initiate at 0.25 mcg/day; titrate every 2 to 4 weeks if needed
Calcifediol	- Secondary hyperparathyroidism in adults with stage 3 or 4 CKD and serum total 25-hydroxyvitamin D levels less than 30 ng/mL - Not for patients with stage 5 chronic kidney disease or end-stage renal disease on dialysis	30 mg ER oral capsules	30 mcg once daily; may increase to 60 mcg once daily after 3 months if needed.
Doxercalciferol	- IV: secondary hyperparathyroidism in patients with CKD on dialysis - Oral: secondary hyperparathyroidism in patients with Stage 3 or 4 CKD	2 mcg and 4 mcg IV sol 1 mcg and 2 mcg oral capsules	IV: 4 mcg TIW at the end of dialysis. Dose may be increased at 8-week intervals by 1-2 mcg Oral: Dialysis patients: 10 mcg TIW; may increase by 2.5 mcg at 8-week intervals if needed (max dose of 60 mcg/week) Pre-dialysis: 1 mcg/day; may increase by 0.5 mcg at 2-week intervals if needed (max dose of 3.5 mcg/day)
Paricalcitol	- IV: secondary hyperparathyroidism associated CKD on dialysis - Oral capsules: secondary hyperparathyroidism associated with stage 3 or 4 CKD	0.04 mcg/kg to 0.1 mcg/kg IV sol 1 mcg, 2 mcg, and 4 mcg oral capsules	IV: given as a bolus dose no more frequently than every other day during dialysis; may increase by 2-4 mcg at 2 or 4 week intervals if needed Oral: 1 or 2 mcg once daily or TIW, dependent on baseline iPTH levels; may increase every 2 or 4 weeks if needed

Abbreviations: CKD = chronic kidney disease; CrCl = creatinine clearance; ER = extended-release; iPTH = intact parathyroid hormone; IV = intravenous; TIW = three times weekly

Parathyroid hormone levels are often used to monitor therapeutic efficacy of vitamin D analogs; however, because inactive and active fragments are measured, assays often have large variations.[3] Levels of intact parathyroid hormone (iPTH) in dialysis patients should be between 150 and 300 pg/mL. However, clinically meaningful outcomes for treatment of vitamin D analogs include reduced risk for bone fractures, bone pain, muscle weakness, need for renal replacement therapy or dialysis, parathyroidectomy, cardiovascular disease, and mortality. Patients who receive vitamin D analogs should be monitored for adverse effects, which include hyperphosphatemia and hypercalcemia. Serum phosphorous levels of 3.5 to 5.5 mg/dL and serum corrected total calcium levels of 8.4 to 9.5 mg/dL are recommended and should be routinely monitored.[1]

Calcitriol is currently the most utilized vitamin D analog in the OHP fee-for-service population.

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.

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), Cochrane Collection, 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.

Systematic Reviews:
Cochrane Collaboration – Vitamin D Compounds and Chronic Kidney Disease Pre-Dialysis
In 2009, the Cochrane Collaboration systematically reviewed evidence for the use of vitamin D compounds and suppression of PTH in patients with CKD not on dialysis.[1] Studies included in the review were randomized controlled trials (RCTs) using vitamin D analogs to manage CKD mineral and bone disorder in patients with CKD not requiring dialysis. Several vitamin D analogs were included in the review but the only agents approved by the FDA used in this review were calcitriol (5 studies), doxercalciferol (1 study), and paricalcitol (1 study). Sixteen RCTs of oral or IV formulations met inclusion criteria. Ten studies were placebo-controlled. Most studies were small (less than 50 participants) with a duration of less than 12 months. All patients had CKD: 2 studies with stage 2 or lower, 8 studies enrolled stage 3 or lower, and 3 studies enrolled stage 4 or lower. The overall quality of most of the studies was poor.

Vitamin D compounds did not reduce mortality (RR 1.40; 95% CI, 0.38 to 5.15) or prevent need for dialysis during the studies (RR 0.76; 95% CI, 0.36 to 1.62).[1] However, vitamin D compounds reduced PTH levels compared to placebo by a mean difference (MD) of -49.34 pg/mL (95% CI, -85.70 to 12.97 pg/mL), based on 4 studies. Vitamin D compounds were also associated with higher phosphorous levels compared to placebo by a MD of 0.37 mg/dL (95% CI, 0.09 to 0.66 mg/dL) and increased serum calcium by a MD of 0.20 mg/dL (95% CI, 0.17 to 0.23 mg/dL). Evidence for reduction in bone fractures, parathyroidectomy and bone pain was insufficient to draw conclusions. Of the 9 studies which reported harms, one study found nausea and vomiting with paricalcitol to be similar to placebo.

There was insufficient comparative evidence between calcitriol and newer vitamin D analogs. Limitations to the analysis included small study sizes so there was likely insufficient power to detect differences in meaningful outcomes (e.g., mortality and morbidity outcomes) between treatments if they do exist.

Cochrane Collaboration – Vitamin D Compounds and Chronic Kidney Disease in Patients Requiring Dialysis

A second systematic review was performed to determine the role of vitamin D compounds in patients with CKD requiring dialysis.[2] The effect of vitamin D compounds on mortality, PTH and bone tissue was investigated. To be included in the review trials had to be RCTS of vitamin D compounds used to manage CKD mineral and bone disorders in patients with CKD and undergoing dialysis. Sixty studies met the inclusion criteria .Among the vitamin D analogs included in the review, calcitriol (7 studies), doxercalciferol (1 study) and paricalcitol (6 studies) were the only agents approved by the FDA. Thirteen studies were head-to-head studies; however, only 2 of these studies evaluated drugs available in the U.S. (n=294). Most studies enrolled less than 75 participants. Pediatric patients were represented in 6 studies. Most studies (n=50) enrolled patients on hemodialysis and 7 studies included patients with peritoneal dialysis. Most studies were deemed to be poor quality.

Meta-analysis was limited due to heterogeneity of study outcomes. No difference in mortality was found between vitamin D analogs and placebo (RR 1.34; 95% CI, 0.34 to 5.24).[2] Rates of bone fracture, bone pain, and effects on stature were similar between vitamin D analogs and placebo; however, the number of outcomes were too low to draw meaningful conclusions. Vitamin D analogs lowered PTH levels but assessment of differences in efficacy between vitamin D analogs was limited. One study found newer analogs similarly lowered PTH levels as older vitamin D analogs (MD 19.0 pg/mL; 95% CI, -96.2 to 134.2 pg/mL). Eight additional studies reported PTH levels but were not reported in a way that allowed for meta-analysis. Placebo-controlled studies found vitamin D analogs lowered PTH levels more than placebo by a MD of -196.05 pg/mL; 95% CI, -298.43 to -93.66 pg/mL). Suppression of PTH levels by 30% or more was accomplished more effectively with vitamin D analogs than placebo (RR 5.90; 95% CI, 3.17 to 10.96). Both newer and established vitamin D analogs suppressed PTH levels by 30% or more by similar extent compared to placebo (RR 2.72; 95% CI, 1.12 to 6.61 and RR 7.05; 95% CI, 3.82 to 13.04, respectively).

Serum phosphorous levels were significantly increased with vitamin D analogs, compared to placebo in data from 2 studies (MD 0.70 mg/dL; 95% CI, 0.08 to 1.33) and hypercalcemia was more common with vitamin D anaolgs compared to placebo (39% vs. 5%; p = 0.070).[2] Newer vitamin D analogs were associated with a higher incidence of hypercalcemia compared to placebo but serum phosphorous data were not reported. Evidence suggests that IV vitamin D analogs may suppress PTH more than oral formulations but evidence is insufficient to draw strong conclusions. There was insufficient evidence on the effect of different dosing strategies on outcomes.

In head-to-head comparisons of vitamin D analogs, no difference in mortality was found based on data from 94 patients.[2] There was insufficient evidence to draw conclusions on bone fracture rates and bone pain. One study of PTH levels found no difference between the newer vitamin D analogs on PTH suppression. Phosphorous levels were also similar between agents. One study found serum calcium levels to be similar between older and newer vitamin D analogs (MD 0.30 mg/dL; 95% CI, -0.11 to 0.71 mg/dL).

Cochrane Collaboration – Interventions for Metabolic Bone Disease in Children with Chronic Kidney Disease

A 2015 systematic review assessed the role of interventions for metabolic bone disease in children with Stage 2 to Stage 5 CKD (including patients on dialysis).[3] Randomized trials evaluating CKD-MBD (stages 2-5, including dialysis patients) in children and adolescents (up to age 21) were included. Eighteen studies were identified (n=576) of children up to the age of 21 years. Interventions included in the studies included dietary interventions, vitamin D compounds and analogs, calcimimetic agents and phosphate-binding agents.

Change in PTH levels was the most commonly investigated outcome with little evidence on growth or bone deformities. Most of the studies had high risk of performance bias. Two studies compared oral versus intraperitoneal calcitriol. One study was too small to draw meaningful conclusions (n=7) and the second found no difference between the types of administration for the outcomes of suppression of PTH, hyperphosphatemia, hypercalcemia or bone histology. Intermittent compared to once daily dosing of calcitriol was evaluated in 3 studies (n=104).[3] PTH levels, height, hypercalcemia and hyperphosphatemia were not statistically different between groups. Six studies compared vitamin D analogs. In placebo-controlled comparisons, IV formulations of calcitriol and paricalcitol were more effective at lowering PTH levels without differences in risk of hypercalcemia. One head-to-head found no significant differences in parameters of bone health when doxercalciferol was compared to calcitriol, on background sevelamer or calcium carbonate. Limitations to this review include the insufficient evidence available on growth rates, bone fracture rates, or cardiovascular calcification. Additionally, many studies were too small to detect a treatment difference if differences in these outcomes did exist.

Paricalcitol Use in Chronic Kidney Disease

The efficacy and safety of paricalcitol was evaluated in a systematic review and meta-analysis of RCTs in patients with Stage 2-5 CKD.[4] The analysis included RCTs of patients with sage 2-5 CKD and any dose or type (oral or IV) of paricalcitol. The Jadad scale score (0-5) and risk of bias were assessed to evaluate the quality of the included trials. Efficacy outcomes studied were proteinuria, PTH suppression, and serum calcium and phosphorous levels. Nine placebo-controlled trials were included (n=832). The majority of studies were of good quality with a Jadad score of greater than 3. Five trials were in patients on hemodialysis and 4 trials were in patients with stage 2-4 CKD. Durations of trials ranged from 4 weeks to 6 months. The primary outcomes were either changes in intact PTH levels, incidence of proteinuria or changes in urine albumin/creatinine ratio.

Four studies (n=469) evaluated the effect of oral paricalcitol compared to placebo on reducing residual albuminuria in patients with CKD on background angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). Use of oral paricalcitol 1-2 mcg/day statistically significantly reduced proteinuria (defined as $\geq$10% reduction in proteinuria) versus placebo (RR 1.68; 95% CI, 1.25 to 2.25; p<0.001).[4] Paricalcitol decreased PTH levels at least 30% from baseline more than placebo (RR 6.37; 95% CI, 4.64 to 8.74; p<0.001) based on 5 trials (n=563). Fifty-six percent of patients were receiving IV paricalcitol and undergoing hemodialysis and 44% were taking oral paricalcitol and had CKD stage 3 and 4. Hypercalcemia was not significantly more common with paricalcitol compared to placebo (RR 2.25; 95% CI, 0.81 to 6.26: p=0.12). Phosphorous levels were only reported in one trial, so meta-analysis was not performed. Risk of harms were reported in 6 trials. Adverse events were not statistically significantly different between paricalcitol and placebo (58 vs. 28; RR 1.28; 95% CI, 0.84 to 1.94; P=0.26). Limitations of the meta-analysis include heterogeneity of the data, such as different primary endpoints studied, use of oral and IV paricalcitol, and lack of evidence on long-term outcomes, such as progression of renal disease, bone fracture rates and mortality.

Clinical Practice Guidelines:

Kidney Disease: Improving Global Outcomes (KDIGO)

In 2012 the KDIGO published their updated recommendations for the management, evaluation and treatment of patients with CKD.[7] The GRADE system was used to evaluate the literature and assign strength of recommendations to the quality of evidence. In addition to the quality of the recommendation, the committee assigned a grade of level 1 or level 2 depending on the evidence. Level 1 evidence was defined as "most patients should receive the recommended course of action" or level 2 defined as "different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences". A Guidance pertaining to use of vitamin D analogs will be presented here. All patients with CKD and an estimated glomerular filtration rate (GFR) of less than 45 mL/min/1.73 m^2 should have serum calcium, phosphate, PTH and alkaline phosphatase levels evaluated based on low quality evidence. Patients with elevated PTH levels should also be tested for hyperphosphatemia, hypocalcemia, and vitamin D deficiency. The

KDIGO do not recommend routinely adding vitamin D supplements or vitamin D analogs in patients with CKD and not on dialysis without documentation of vitamin D deficiency or elevated PTH levels based on level 2 moderate quality of evidence.

National Institute for Health and Care Excellence (NICE)

Recommendations for management of adults with CKD were updated by NICE in 2014.[15] Recommendations related to CKD and treatment with vitamin D analogs include measurement of calcium, phosphorous, PTH and vitamin D levels should be performed only in patients with a GFR less than 30 mL/min/1.73 m^2. Routine vitamin D supplementation should not be used to manage CKD-mineral and bone disorders. Cholecalciferol or ergocalciferol supplements are recommended to treat vitamin D deficiency in CKD; however, if symptoms of CKD-mineral and bone disorders persist after correction of vitamin D deficiency, alfacalcidol (not available in the US) or calcitriol are recommended to patients with a GFR less than 30 mL/min/1.73 m^2. Serum phosphate and calcium levels should be routinely monitored in patients receiving vitamin D supplements or analogs.

Veterans Affairs/Department of Defense (VA/DoD) Clinical Practice Guideline for the Management of Chronic Kidney Disease in Primary Care

An update of the 2007 VA/DoD guideline on the management of CKD in primary care was published in 2014.[16] Clinical management strategies pertaining to the use of vitamin D analogs include a weak recommendation to not have primary care physicians prescribe vitamin D analogs in patients with Stage 3 and 4 CKD with elevated PTH levels. This recommendation is based on the lack of evidence of kidney, bone or cardiovascular benefit for broad use. Referral to a nephrologist is recommended for management of vitamin D analogs.

Randomized Controlled Trials:

There are a limited number of high quality RCTs evaluating vitamin D analogs. Comparative studies of effectiveness between the different vitamin D compounds are of interest and available evidence is presented below in Table 2.

Table 2. Summary of Direct Comparative Studies Completed

Study	Comparison	Population	Primary Outcome	Results
Coyne, et al[17] PG, RCT, MC, OL 24 weeks	paricalcitol 1 mcg/day* vs. calcitriol 0.25 mcg/day*	Patients with Stage 3-4 CKD and secondary hyperparathyroidism N= 110	Hypercalcemia ≥10.5 mg/dL	Paricalcitol: 3 (6%) calcitriol: 1 (2%) p =0.36
Ong, et al[5] PG, RCT, OL 24 weeks	oral paricalcitol daily ǂ vs. oral calcitriol daily ǂ ǂ Dose based on iPTH levels and titrated every 3 weeks to obtain an iPTH level of 150-300 pg/mL	Patients with secondary hyperthyroidism on dialysis N=66	≥30% reduction in iPTH	paricalcitol: 22 (61.1%) calcitriol: 22 (73.3%) p =0.29
Abbreviations: CKD = chronic kidney disease; iPTH = intact parathyroid hormone; MC = multi-center; OL = open-label; PG = parallel group; RCT = randomized controlled trial * Initial dose				

NEW DRUG EVALUATION

Clinical Efficacy:

Extended-release calcifediol was studied in 2 identical placebo-controlled, double-blind, Phase 3 RCTs in a total of 429 patients with stage 3 or 4 CKD and secondary hyperparathyroidism.[6] Patients were randomized to ER calcifediol 30 or 60 mcg daily at bedtime or placebo. The mean age of patients was 66 years with a mean iPTH level of 147.2 pg/mL. The primary outcome was a 30% or greater reduction in PTH level from baseline at 26 weeks. Secondary outcomes were incidence of hypercalcemia, defined as 2 consecutive serum calcium values of more than 10.3 mg/dL, and hyperphosphatemia, defined as 2 consecutive serum phosphorous levels more than 5.5 mg/dL. Secondary outcomes had to be deemed to be related to the study drug, which may introduce bias since hypercalcemia and hyperphosphatemia are known adverse effects of vitamin D analogs. The first trial found PTH levels reduced by more than 30% in 33% of patients taking ER calcifediol compared to 8% taking placebo ($p<0.001$, CI not provided; NNT 4 over 26 weeks) (Table 4). The second study found 34% of patients in the ER calcifediol group and 7% in the placebo group obtained the primary endpoint ($p<0.001$, CI not provided; NNT 4)(Table 4).[6] Lack of details on study methodology limit the strength of evidence of these findings and suggest the potential for high risk of bias. Long-term studies of health outcomes (i.e., mortality, bone fracture rates, parathyroidectomy, etc.) would be more helpful to determine the benefit of ER calcifediol.

Clinical Safety:

At total of 5.7% of patients in the ER calcifediol group discontinued the first trial early due to adverse events compared to 2.8% in the placebo group.[6] In the second study, discontinuation rates due to adverse events were 4.9% in the ER calcifediol group and 5.6% in the placebo group.[6] Adverse events occurring more commonly with ER calcifediol compared to placebo are presented in Table 3. Six patients who received ER calcifediol experienced hypercalcemia compared to none in the placebo groups based on a pooled data analysis of both studies. The incidence of hyperphosphatemia was 0.4% in the ER calcifediol groups compared to 0% in the placebo group based on pooled data.

Table 3. Adverse Events Occurring in ≥ 1.4% of Patients Treated with ER Calcifediol Compared to Placebo[11]

Adverse Reaction	Placebo (n=144)	ER Calcifediol (n=285)
Anemia	3.5%	4.9%
Nasopharyngitis	2.8%	4.9%
Blood creatinine increase	1.4%	4.9%
Dyspnea	2.8%	4.2%
Cough	2.1%	3.5%

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:

1) Mortality
2) Bone fractures
3) Requirement for dialysis
4) Reduction in PTH

Primary Study Endpoint:

1) Reduction in PTH

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. Sprague, et al.[6] RCT, DB, PC, MC 26 weeks	1. ER Calcifediol 30 or 60 mcg daily (C)* 2. Placebo daily (P) ER Calcifediol dose was 30 mcg for 12 weeks and then 30-60 mcg for 14 weeks. Dose was based on iPTH, vitamin D and calcium levels	Demographics: Age: 65 years Male: 52% White: 63% eGFR: 31 mL/min/1.73 m^2 iPTH: 144.5 pg/mL 25-hydroxyvitamin D: 19.7 ng/dL Key Inclusion Criteria: - iPTH >70 pg/mL - 25-hydroxyvitamin D <30 ng/mL - Stage 3-4 CKD - Age ≥18 years - eGFR ≥15 to <60 ml/min/1.73 m2 - 25-hydroxyvitiman D ≥ 10 ng/dL - plasma iPTH ≥ 85 and < 500 pg/ml - Serum Ca ≥8.4 to <9.8 mg/dL - P ≥2.0 to <5.0 mg/dL Key Exclusion Criteria: - Ca:SCr ratio >0.2 - Nephrotic proteinuria (SCr >3 mg/mL) -Parathyroidectomy for SHPT - Renal transplant - Dialysis - Bone metabolism therapy	ITT: C: 141 P: 72 Attrition: C: NR P: NR	Primary Endpoint: Reduction in iPTH ≥30%: C: 47 (33%) P: 8 (8%) (CI not provided) p<0.001 Secondary Endpoints:	25%/4	Hypercalcemia*: C: 6 (2%) P: 0 (0%) p-value NR Hyperphosphatemia*: C: 1 (0.4%) P: 0 (0%) p-value NR Discontinuations due to AE: C: 8 (5.7%) P: 2 (2.8%) p-value NR Anemia*: C: 7 (4.9%) P: 3 (3.5%) p-value NR Increased SCr*: C: 7 (4.9%) P: 1 (1.4%) p-value NR * Only pooled data from Study A and B was reported	NA NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (unclear) randomized 2:1, process not described. Performance Bias: (low) blinding of subjects and staff described and maintained allocation concealment. Detection Bias: (unclear) details on outcome assessment was not provided. Attrition Bias: (unclear) 17% of patients from both studies discontinued but details were not provided. True ITT analysis was used and dropouts were categorized as non-responders. Reporting Bias: (unclear) Pre-specified outcomes reported. Study funded by manufacturer. **Applicability**: Patient: Patients are representative of those requiring vitamin D analogs and not requiring dialysis. Intervention: Labeled doses of 30 to 60 mcg daily administered. Comparator: Placebo comparison appropriate to establish efficacy. Outcomes: pre-specified surrogate outcomes measured. Outcomes such as mortality, need for renal replacement therapy and fractures would help to better inform treatment decisions. Setting: Eighty-nine US sites (both studies).

2. Sprague, et al.[6] RCT, DB, PC, MC 26 weeks	1. ER Calcifediol 30 or 60 mcg daily (C)* 2. Placebo daily (P) ER Calcifediol dose was 30 mcg for 12 weeks and then 30-60 mcg for 14 weeks. Dose was based on iPTH, vitamin D and calcium levels	Demographics: Age: 66 years Male: 48% White: 66% eGFR: 31 mL/min/1.73 m^2 iPTH: 151.6 pg/mL 25-Hydroxyvitamin D: 19.6 ng/dL Key Inclusion Criteria: See above Key Exclusion Criteria: See above	ITT: C: 144 P: 72 Attrition: C: NR P: NR	Primary Endpoint: Reduction in iPTH levels by at least 30%: C: 49 (34%) P: 5 (7%) (CI not reported) p<0.001 Secondary Endpoints:	 27%/4	See above		**Risk of Bias (low/high/unclear)**: Selection Bias: (unclear) see above. Performance Bias: (low) see above. Detection Bias: (unclear) see above. Attrition Bias: (unclear) see above. Reporting Bias: (unclear) see above. **Applicability**: Patient: see above. Intervention: see above. Comparator: see above. Outcomes: Outcomes: see above. Setting: see above.

Abbreviations [alphabetical order]: ARR = absolute risk reduction; Ca = calcium; CI = confidence interval; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; iPTH = intact parathyroid hormone ITT = intention to treat; MC – multi-center; mITT = modified intention to treat; MR = modified release; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; P = phosphorous; PP = per protocol; SCr = serum creatinine; SHPT = secondary hyperparathyroidism.

References:

1. Palmer SC, McGregor DO, Craig JC, Elder G, Macaskill P, Strippoli GF. Vitamin D compounds for people with chronic kidney disease not requiring dialysis. *Cochrane Database Syst Rev*. 2009;(4):CD008175. doi:10.1002/14651858.CD008175.

2. Palmer SC, McGregor DO, Craig JC, Elder G, Macaskill P, Strippoli GF. Vitamin D compounds for people with chronic kidney disease requiring dialysis. *Cochrane Database Syst Rev*. 2009;(4):CD005633. doi:10.1002/14651858.CD005633.pub2.

3. Hahn D, Hodson EM, Craig JC. Interventions for metabolic bone disease in children with chronic kidney disease. *Cochrane Database Syst Rev*. 2015;(11):CD008327. doi:10.1002/14651858.CD008327.pub2.

4. Cheng J, Zhang W, Zhang X, Li X, Chen J. Efficacy and safety of paricalcitol therapy for chronic kidney disease: A Meta-Analysis. *CJASN*. 2012;7(3):391-400. doi:10.2215/CJN.03000311.

5. Ong LM, Narayanan P, Goh HK, et al. Randomized controlled trial to compare the efficacy and safety of oral paricalcitol with oral calcitriol in dialysis patients with secondary hyperparathyroidism. *Nephrology*. 2013;18(3):194-200. doi:10.1111/nep.12029.

6. Sprague SM, Crawford PW, Melnick JZ, et al. Use of extended-release calcifediol to treat secondary hyperparathyroidism in stages 3 and 4 chronic kidney disease. *Am J Nephrol*. 2016;44(4):316-325. doi:10.1159/000450766.

7. Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO 2012 clinical practice guideline. *International Society of Nephrology*. 2013;3(1):S1-S163. http://www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf. Accessed November 8, 2016.

8. Han T, Rong G, Quan D, et al. Meta-Analysis: The efficacy and safety of paricalcitol for the treatment of secondary hyperparathyroidism and proteinuria in chronic kidney disease. *BioMed Research International*. 2013;2013:1-11. doi:10.1155/2013/320560.

9. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *JASN*. 2004;15(8):2208-2218. doi:10.1097/01.ASN.0000133041.27682.A2.

10. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. Diagnosis of CLD-MBD: biochemical abnormalities. *Kidney international Supplement*. 76 (Suppl 113):S22-S49. doi:10.1038/ki.2009.191.

11. Rayaldee (calcifediol). Miami, FL: OPKO Pharmaceuticals, LLC, 2016.

12. Zemplar (paricalcitol). North Chicago, IL: AbbVie Inc., October 2016.

13. Hectoral (doxercalciferol). North Chicago, IL: Abbott Laboratories, May 2005.

14. Rocaltrol (calcitrol). Parsippany, NJ: Validus Pharmaceuticals LLC, August 2010.

15. National Institute for Health and Care Excellence. Chronic kidney disease in adults: assessment and management. *National Institute for Health and Care Excellence Clinical Guideline*. July 23, 2014 https://www.nice.org.uk/guidance/cg182?unlid=616689932016111443858. Accessed December 5, 2016.

16. Veterans Administration Department of Defense. VA/DoD clinical practice guideline for the management of chronic kidney disease in primary care. *Veterans Administration Department of Defense Guideline Summary.* November 2000 (Revised December 2014). www.guideline.gov/summaries/summary/48951/vadod-clinical-practice-guideline-for-the-management-of-chronic-kidney-disease-in-primary-care?q=vitamin+d+analogs. Accessed November 8, 2016.

17. Coyne DW, Goldberg S, Faber M, Ghossein C, Sprague SM. A randomized multicenter trial of paricalcitol versus calcitriol for secondary hyperparathyroidism in stages 3-4 CKD. *Journal of The American Society of Nephrology*. 2014;9(9):1620-1626. doi:10.2215/CJN.10661013.

Appendix 1: Specific Drug Information

Table 5. Clinical Pharmacology and Pharmacokinetics

Drug Name	Mechanism of Action	Absorption	Metabolism/Excretion	Pharmacokinetics (mean)
Calcitriol (Rocaltrol®)	Synthetic vitamin D analog which regulates absorption of calcium from the GI tract and utilization throughout the body.	Rapidly absorbed from the intestine	• 24-hydroxylase and hydroxylation • enterohepatic recycling and biliary excretion	• Half-life: 5-8 hours • Cmax: not provided • AUC: 60 pg/mL at 2 • Vd: not provided • 99% protein bound
Doxercalciferol (Hectoral®)	Synthetic vitamin D analog that undergoes activation to the biologically active form of vitamin D2.	Rapidly absorbed from the intestine	• Metabolized by CYP27 in the liver and by hydroxylation in the kidney	• Half-life: 32-37 hours • Cmax: at 11-12 hours (levels not provided) • AUC: 60 pg/mL • Vd: not provided
Paricalcitol (Zemplar®)	Synthetic vitamin D2 analog of calcitriol resulting in reduced PTH synthesis and secretion.	72-86%	• Metabolized by CYP24, CYP3A4 and UGT1A4 • Excreted in the feces	• Half-life: 4-6 hours • Cmax: not provided • AUC: not provided • Vd: 34 L • >98% protein bound
Calcifediol (Rayaldee®)	Converted to calcitriol in the kidney resulting in increased intestinal absorption of calcium and phosphorous and decreased PTH synthesis.	Increased absorption with high fat, high calorie meal	• Metabolized by CYPP450 primarily in the kidney • Excreted by fecal and biliary route	• Half-life: 11 days • Cmax: not provided • AUC: not provided • Vd: 8.8. L • >98% protein bound

Use in Specific Populations:
Calcitriol: use in patients with renal insufficiency (nephrotic syndrome and undergoing dialysis) were found to have lower pre-dose and peak calcitriol levels with at least double the half-life compared to normal subjects. No specific dosing recommendations were provided.
Calcifediol: use in pediatric patients has not been studied.
Doxercalciferol: use in pediatric patients has not been studied. Use with caution in patients with impaired hepatic function.
Paricalcitol: not recommended to be used during breast feeding.

Drug Safety:
FDA Boxed Warnings:
There are no FDA boxed warnings for vitamin D analogs.

Contraindications:

Calcifediol: none
Calcitriol, doxercalciferol and paricalcitol: do not use in patients with hypercalcemia or evidence of vitamin D toxicity.

Table 6. Summary of Warnings and Precautions

Warning/Precaution	Calcitriol	Doxercalciferol	Paricalcitol	Calcifediol
Hypercalcemia	X	X	X	X
Hyperphosphatemia		X		
Adynamic bone disease				X
Digitalis toxicity			X	X
Increased serum creatinine	X			
Over-suppression of PTH		x		
Aluminum overload			X	

Appendix 2: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) without Revisions** 1996 to November Week 3 2016

Search Strategy:

#	Searches	Results	Annotations
1	Calcitriol/	7143	
2	paricalcitol.mp.	478	
3	calcifediol.mp. or Calcifediol/	1918	
4	doxercalciferol.mp.	79	
5	1 or 2 or 3 or 4	9039	
6	limit 5 to (english language and humans)	6488	
7	limit 6 to (clinical trial, all or clinical trial or comparative study or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)	1561	
8	limit 7 to yr="2007 -Current"	739	

Drug Use Research & Management Program
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Phone 503-947-5220 | **Fax** 503-947-1119

New Drug Evaluation: Obeticholic acid (Ocaliva®) film-coated oral tablet

Date of Review: January 2017
Generic Name: Obeticholic acid
PDL Class: unassigned

End Date of Literature Search: September 23, 2016
Brand Name (Manufacturer): Ocaliva® (Intercept Pharmaceuticals, Inc)
AMCP Dossier Received: Yes

Current Status of PDL Class: unassigned

Research Questions:

- What is the efficacy of obeticholic acid compared to currently available agents or is it superior to placebo for treatment of non-alcoholic steatohepatitis (NASH) and primary biliary cholangitis (PBC)?
- Is obeticholic acid safe for treatment of NASH or PBC?
- Are there any subgroups (i.e. age, gender, ethnicity, concomitant diabetes, disease duration or severity) that would particularly benefit or be harmed from treatment with obeticholic acid?

Conclusions:

- There is low quality evidence based on one phase 3 and one phase 2 clinical trial that obeticholic acid improves alkaline phosphatase (ALP) levels in patients with PBC and inadequate response to ursodeoxycholic acid (UDCA), also known as ursodiol. The majority of patients included in these trials were white females with normal bilirubin levels and a mean ALP of 323 units/L. Response to obeticholic acid (defined as ALP <1.67-times the upper limit of normal (ULN), ALP decrease >15%, and bilirubin level within normal limits) was achieved at 3 months in 41% (43/105) of patients taking obeticholic acid 10 mg daily in combination with ursodiol compared to 5% (5/106) of patients taking placebo (number needed-to-treat [NNT] =3).[1] Over 90% of participants remained on ursodiol during the trials.
- There is low quality evidence from a pooled analysis of clinical trial data conducted by the FDA that obeticholic acid improves ALP levels in patients with PBC intolerant to ursodiol. At 3 months, response to therapy (as defined above) was achieved in 35% (10/26) of patients taking obeticholic acid compared to 4% (1/28) of patients taking placebo.[1] Data is limited by the number of patients included in these trials and stringent criteria excluding patients with severe disease.
- Use of ursodiol at 13-15 mg/kg/day as first-line therapy for PBC has demonstrated decreased disease progression and increase time to liver transplantation.[2] There is insufficient evidence to evaluate long-term efficacy of obeticholic acid for PBC or evaluate efficacy in specific subgroups. The U.S. Food and Drug Administration (FDA) requires drug labeling to caution that continued approval for PBC may be contingent upon verification and description of clinical benefit in confirmatory trials.[3]
- There is insufficient evidence to evaluate efficacy or safety of obeticholic acid for off-label treatment of NASH. Clinical trial data are limited by small population sizes, use of un-validated surrogate endpoints, and lack of long-term outcomes.

- The FDA labeling includes warnings for severe pruritus and liver-related adverse effects. Severe pruritus occurred in 7%, 19%, and 23% of patients taking placebo, 5 to 10 mg of obeticholic acid, and 10 mg obeticholic acid, respectively.[1] Obeticholic acid use was also associated with a numerically greater number of liver-related adverse effects including new onset jaundice, ascites, PBC flares and biochemical changes typically indicative of hepatic injury.[1] Patients with complications from cirrhosis or hepatic decompensation were excluded from these trials. There is insufficient evidence to evaluate long-term safety of obeticholic acid for the treatment of PBC or NASH and long-term data are needed to determine the significance of harms observed in short-term phase 2 and 3 trials.

Recommendations:

- Recommend incorporation of the STC 05 Bile Therapy drugs (obeticholic acid, ursodiol, and cholic acid) into one PDL class.
- Recommend ursodiol as a preferred medication and obeticholic acid as a non-preferred medication due to the lack of long-term efficacy and safety data. No recommendations are made for other bile therapy medications at this time.
- Recommend the proposed PA criteria for all non-preferred drugs which encourages use of ursodiol as first-line therapy and restricts obeticholic acid use to populations that may benefit from this therapy without undue harm (**Appendix 2**).

Background:

Obeticholic acid is a drug which recently achieved accelerated approval by the FDA for treatment of primary biliary cholangitis (PBC; also known as primary biliary cirrhosis). It binds to the farnesoid X receptor in liver and intestinal cells which results in decreased production of bile and increased bile flow from the liver. Obeticholic acid currently does not have FDA approval for treatment of other liver conditions. However, it has been granted a breakthrough therapy designation from the FDA for nonalcoholic steatohepatitis (NASH).[4] Drugs may be designated as breakthrough therapy if preliminary evidence indicates they may demonstrate substantial improvement over available therapy for a serious condition.[5] Improvements can include clinically relevant endpoints, surrogate endpoints or change in pharmacodynamics biomarkers which indicate a potential for improved disease outcomes.[5] Because NASH is a common disease with few disease-altering treatment options, there is a large potential for off-label use of obeticholic acid. This review examines the evidence supporting efficacy and safety of obeticholic acid for treatment of PBC and for off-label treatment of NASH. Currently, bile therapies (including ursodiol, obeticholic acid, chenodiol, and cholic acid) have not been assigned to a preferred or non-preferred PDL status.

Primary biliary cholangitis is a relatively rare disease thought to be autoimmune in origin. PBC affects approximately 1.91 to 40.2 per 100,000 people and is most common in women.[1] It is characterized by anti-mitochondrial auto-antibodies which target biliary epithelial cells and cause antibody-mediated destruction of intrahepatic bile ducts and liver cells.[2] Clinically, elevation of a group of enzymes called alkaline phosphatase (ALP) is associated with biliary disease.[6] These enzymes are found in many body tissues including liver, bone, small intestine, kidneys, placenta and leukocytes.[6] In adults, about 80% of ALP found in serum comes from liver and bone tissue.[6] The mechanism of hepatic ALP release into circulation in patients with cholestatic disease is unclear but bile accumulation appears to increase hepatocyte synthesis of ALP.[6] Elevations of ALP more than 4-times ULN suggests a cholestatic disorder but lesser elevations (around 3-fold ULN) are relatively nonspecific and can occur in all types of liver disease, while mild elevations less than 1.5-times normal can be seen in normal patients without disease.[6] Diagnosis is based on presence of at least 2 of the following factors: evidence of chronic cholestasis such as persistently elevated ALP greater than 1.5-times ULN for more than 6 months, presence of anti-mitochondrial antibodies, or histological evidence of PBC upon biopsy.[2] Without treatment, progressive damage to biliary cells causes inflammation and eventually leads to fibrosis and liver failure. Prognosis varies depending on disease severity and duration. In patients with early stage disease, approximately 50% develop cirrhosis within 4 years and 15-25% develop liver failure within 5 years.[2] In another study of asymptomatic patients with PBC, the 10-year survival rate ranged from 50-70%.[2] In symptomatic patients, median survival time was 5 to 8 years after symptom

onset.[2] Factors that increase risk of progressive cirrhosis include bilirubin levels greater than 1 mg/dL and moderate to severe lymphocytic piecemeal necrosis upon biopsy.[2]

Prior to 2016, the only FDA approved medication for treatment of PBC was ursodiol. Use of ursodiol at 13-15 mg/kg/day has demonstrated decreased disease progression and increase time to liver transplantation.[2] Guidelines from the American Association for the Study of Liver Disease recommend ursodiol as a first-line therapy regardless of histologic stage.[2] Typically, improvement in liver function tests (LFTs) is seen within 2 weeks of starting therapy.[2] Further improvement can be observed over 6-9 months, though in some patients LFTs may continue to improve over the course of 2-5 years.[2] Common adverse effects of ursodiol include loose stools, headache and mild weight gain. Approximately 3% of patients are intolerant to therapy.[2,7] In addition, approximately 40% of patients have an inadequate response to ursodiol.[7] Inadequate or lack of response has previously been defined using multiple parameters. The current FDA-recommended definition of inadequate or non-response in PBC is less than 40% reduction in ALP levels at 12 months if baseline ALP levels are greater than 2-times ULN or a reduction less than 15% at 12 months if baseline ALP levels are between 1.67- and 2-times ULN.[1,7] These patients have a higher risk of disease progression and may benefit from further therapy to lower ALP levels and prevent long-term outcomes.[7] Standard therapy for patients with PBC also includes immunizations against hepatitis A and B, alcohol avoidance, symptom management, and prevention or treatment of cirrhosis complications.[2]

Obeticholic acid is indicated for PBC in combination with ursodiol in patients with inadequate response to therapy or as monotherapy in patients unable to tolerate ursodiol due to unacceptable adverse effects. It was approved on the basis of 2 phase 2 and one phase 3 RCT examining reduction in ALP levels. Validity of ALP as a surrogate endpoint can vary depending on the type and stage of liver disease, and correlation in later stages of PBC remains unclear.[7] In a retrospective analysis of patients taking ursodiol for PBC, patients with higher ALP levels one year after diagnosis were correlated with decreased survival at 10 years (84% in patients with ALP ≤2-times ULN vs. 64% in patients with ALP >2-times ULN).[8] Bilirubin levels above ULN are also correlated with reduced transplant-free survival at 10 years (86% with normal bilirubin vs. 41% bilirubin >ULN).[8] However, optimum reduction of ALP levels with treatment of PBC remains unclear and the minimum clinically important reduction in ALP has not been established for PBC. Criteria used in the phase 3 trial were based on the FDA-recommended definition of response (ALPO <1.67x ULN, ALP decrease >15%, and bilirubin ≤ULN). These levels were chosen based on retrospective analyses of ursodiol-treated patients which demonstrated that these specific ALP levels had greatest correlation with transplant-free survival.[1] Direct data evaluating clinically relevant outcomes such as mortality or liver disease progression has not been evaluated. Continued approval for PBC may be contingent upon future studies examining these outcomes.[3]

Nonalcoholic steatohepatitis is a form of nonalcoholic fatty liver disease (NAFLD) caused by an accumulation of triglycerides in the liver. NASH is estimated to be present in approximately 5% of the United States (U.S.) population and is strongly correlated with obesity.[9] Without treatment, approximately 11% of patients will develop cirrhosis over 15 years.[9] NASH is the also the most common cause of hepatocellular carcinoma in the U.S., and an estimated 7% of patients with cirrhosis due to NASH will develop carcinoma within 6.5 years.[9] Current standard of care for NASH includes lifestyle interventions, control of metabolic diseases such as diabetes, and use of vitamin E. However, current pharmacotherapy has not demonstrated improvement in disease progression or other long-term outcomes. Obeticholic acid represents one therapy which has the potential to modify disease progression, but current evidence is limited to 2 phase 2 trials. The primary outcomes examined in these trials were insulin sensitivity in patients with concomitant diabetes and the NAFLD activity score. The NAFLD activity score evaluates NASH severity based on histological assessment with scores ranging from 0 to 8.[10] Scores are assigned based on the following categories: steatosis (0-3), lobular inflammation (0-3), and hepatocellular ballooning (0-2).[9] Fibrosis stage is not included in the NAFLD activity score and is determined separately. The NAFLD activity score has not been correlated with long-term outcomes in PBC, and the minimally important clinically significant difference has not been determined.

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

Clinical Efficacy:

Primary Biliary Cholangitis

Obeticholic acid for treatment of PBC was approved on the basis a 12-month phase 3 placebo-controlled trial and 2 supporting 3-month phase 2 dose-response trials. Response to obeticholic acid was defined as a composite endpoint of ALP less than or equal to 1.67-times ULN, a total bilirubin within normal limits, and an ALP decrease of at least 15% from baseline.[1] Criteria were chosen based on retrospective analyses demonstrating these specific ALP levels had greatest correlation with clinical outcomes of transplant-free survival.[1] Secondary outcomes for these trials included evaluation of other liver function tests and adverse effects associated with therapy.

The majority of patients enrolled in these trials were white females taking concomitant ursodiol therapy. Of the patients enrolled in the phase 3 trial (n=216), only 16 patients (7%) were taking obeticholic acid as monotherapy.[11] Phase 2 trials included an additional 59 patients who took obeticholic acid as monotherapy. Due to stringent inclusion and exclusion criteria, the majority of patients enrolled in these trials had mild or early disease.[11] Patients with bilirubin greater than 2-times ULN, decompensated liver disease or complications of cirrhosis, were excluded from the trials.[11,12] Mean baseline ALP in the phase 3 trial was 323 units/L (less than 3-times ULN), and 92% of patients had a bilirubin level within normal limits.[1,11] Patients enrolled in phase 2 trials had similar baseline disease severity.

Overall, the phase 3 study used for FDA approval had low risk of bias. The study was adequately randomized and blinded with balanced baseline characteristics. Overall, attrition was low but was more common in treatment groups.[11] Missing data in the phase 3 trial were classified as non-responders providing a more conservative estimate of treatment effect.[11] Risk of reporting bias was low, and data analyses were performed by a contracted research company. Phase 2 trials were similarly designed.[12] One phase 2 trial evaluating monotherapy for obeticholic acid remains unpublished. Data from this unpublished trial were included in the FDA summary review but limited information concerning trial design was available from the literature.[1] The phase 2 trials also had higher attrition rates with more frequent discontinuations associated with higher doses of obeticholic acid.[12] Data available from the published phase 2 trial were also imputed using last observation carried forward which may increase risk of bias by overestimating the treatment effect of obeticholic acid.[12]

FDA analysis for efficacy included only patients taking the approved dose of 5 or 10 mg.[1] In phase 2 and 3 trials, response to therapy was achieved at 3 months in 41% (43/105) of patients taking obeticholic acid 10 mg once daily in combination with ursodiol compared to 5% (5/106) of patients taking placebo and ursodiol.[1] In patients taking obeticholic acid 10 mg as monotherapy, 35% (10/26) of patients responded to treatment (see definition above) compared to 4% (1/28) of patients taking placebo.[1] A similar effect was observed at 12 months, with 46-47% of patients achieving a response with obeticholic acid 10 mg daily monotherapy compared to 10% of patients taking placebo.[1,11] Sensitivity analyses using worse case scenarios and more stringent thresholds of response demonstrated similar benefits with obeticholic acid.[1] Because the majority of patients enrolled in these trials had a normal bilirubin level at baseline, the composite outcome was primarily driven by the change in ALP. Similar reductions were observed with gamma-glutamyl transpeptidase (GGT) and aspartate aminotransferase (AST) levels compared to baseline.[1] Because the majority of patients enrolled in these trials had early or mild disease, the applicability of this evidence to patients with more severe disease is limited. In a systematic review conducted by the Institute for Clinical and Economic Review including data from these 3 trials, subgroup analyses based on disease severity were conducted.[7] Results from these analyses indicate that patients with abnormal bilirubin at baseline (n=21) had significant reductions compared to placebo at 12 months (-0.5 mg/dL vs. 0.04 mg/dL, respectively; $p<0.05$) though differences were not observed initially at 3 months.[7] In addition, stratification based on ALP levels demonstrated persistent ALP reduction in patients with baseline ALP levels

between 1-2-times ULN up to values greater than 4-times ULN.[7] These results must be interpreted with caution because of the limited number of patients included in these analyses and because data were primarily drawn from unpublished conference abstracts and poster presentations. In addition, these trials enrolled a limited number of patients who were taking obeticholic acid as monotherapy. The FDA notes that the results from these trials provide preliminary data supporting use of obeticholic acid as monotherapy in PBC but that additional confirmatory trials should be conducted.[1] Recommended post-marketing requirements for the drug include trials to confirm efficacy and safety as monotherapy for PBC, analysis of efficacy and safety in patients with more severe liver disease or hepatic impairment, and confirmation of an association with long-term clinical outcomes such as disease progression, complications of cirrhosis, transplantation, and mortality.[1] Further post-marketing requirements include development of a daily dose formulation for patients with hepatic impairment and participation in the Risk Evaluation and Mitigation Strategies program.[1]

Nonalcoholic Steatohepatitis

The majority of evidence to support the off-label use of obeticholic acid 25 mg daily for treatment of NASH comes from one phase 2, randomized, double-blind placebo-controlled trial (FLINT) that examined improvement in liver histology over the course of 72 weeks (n=238).[10] Results from a smaller phase 2 trial in patients with NASH and diabetes also provide supporting evidence for off-label use of obeticholic acid for NASH.[9] The primary endpoint in the FLINT trial was improvement in the NAFLD activity score of at least 2 points without worsening of fibrosis.[10] Other secondary, clinically-relevant endpoints included improvement in fibrosis stage, liver function tests, health-related quality of life, and adverse effects.[10]

Patients included in the FLINT trial were an average age of 52 years; 80% had a definite diagnosis of NASH, 53.5% had diabetes and more than 60% had hypertension and hyperlipidemia.[10] Patients were included in the trial if they had a total NAFLD activity score of at least 4 of 8 total points with at least 1 point in each category of steatosis, lobular inflammation, and hepatocellular ballooning.[10] Mean fibrosis stage at baseline was 1.9 (SD 1.1) and approximately 22% of patients evaluated had stage 3 fibrosis. Patients were excluded if they had other liver or biliary disease, alcohol or substance abuse, hepatic decompensation, HIV, or diabetes with a hemoglobin A1c greater than 9.5%.[10]

Risk of bias in this trial was low with adequate randomization, blinding and reporting. Risk of attrition bias was high because positive results at an interim analysis resulted in early discontinuation of biopsies for the primary outcome. Biopsies to assess histological improvement of NASH were not performed in 64 patients.[10] Exclusion of these patients from the analysis may result in more favorable efficacy outcomes for the drug. However, of the patients with a biopsy upon study completion, more patients treated with obeticholic acid had improved liver histology (measured by NAFLD activity score) compared with placebo (RR 2.2, 95% CI 1.4 to 3.3, p=0.0002; ARR 24%; NNT 4).[10] Clinical implications of this change are unclear as the NAFLD activity score has not been correlated with clinical outcomes and a minimum clinical important difference has not been determined. Similarly, fibrosis scores improved in patients treated with obeticholic acid compared to placebo (RR 2.0, 95% CI 1.2 to 3.4; p=0.004; NNT=6).[10] However, resolution of NASH with persistent NAFLD or resolution of NAFLD failed to reach statistical significance (RR 1.7, 95% CI 0.9 to 3.2; p=0.08), and there was no difference in health-related quality of life scores between groups.[10]

Overall, these results demonstrate obeticholic acid may be a potential therapy for improvement of NASH. However, evidence is limited by limited a sample size, short duration, and lack of long-term clinical outcomes of cirrhosis. Discontinuations due to adverse events were not reported in the FLINT trial, but other studies have demonstrated higher rates of pruritus with higher doses. These adverse effects may be especially important when determining long-term adherence to therapy. Though these early trials demonstrate potential for use of obeticholic acid for treatment of NASH, many questions remain regarding the long-term efficacy and adverse effects. In addition, use of surrogate endpoints limits applicability of current evidence. Further trials will need to be conducted to establish efficacy in NASH and better evaluate safety of this therapy in NASH.

Clinical Safety:

Safety analyses included all patients from phase 2 and 3 trials with supporting data from trials in healthy volunteers, extension studies, and studies for treatment of NASH. The most common adverse event observed in clinical trials was pruritus occurring in 38% of placebo patients, 56% in patients titrated from 5 mg to 10mg obeticholic acid, and 68% in patients given 10 mg obeticholic acid.[13] Severe pruritus occurred in 7%, 19%, and 23% of patients in the placebo group, obeticholic acid titration group, and 10 mg obeticholic acid group, respectively.[13] Management strategies employed in these trials included use of bile acid sequestrants, anti-pruritic agents, drug holidays, dose reductions and gradual titrations.[1] Pruritus was also the most common reason for treatment discontinuation. A dose dependent decrease in high density lipoprotein (HDL-C) was also observed with obeticholic acid.[13] Mean decrease in HDL-C in 10 mg treatment groups was approximately 10-20 mg/dL from a baseline of 70-80 mg/dL.[1] The clinical implications of this decrease remain uncertain as cardiovascular adverse events were not compared in these short-term trials. However, given the large change in HDL-C, further monitoring and evaluation may be warranted. Serious adverse events were also more common in patients taking obeticholic acid compared to placebo. In patients taking 10 mg obeticholic acid, the rate of serious adverse events was 5.2 events per 100 patient years compared to 2.4 events in the placebo group.[3] In addition, incidence of hepatic adverse events was more common in patients taking obeticholic acid compared to placebo. Rates of hepatic adverse events for placebo, 5 to 10 mg titration, and 10 mg groups were 2.4%, 4.5% and 5.2%, respectively.[13] These events even more frequently at higher doses of 25 mg and 50 mg (above approved 5 and 10 mg dose).[1] Events included new onset jaundice, ascites, PBC flares, and biochemical changes typically indicative of hepatic injury.[13] These events may be due to progressive disease though the imbalance between treatment and placebo groups indicates these adverse events could be drug-related. These adverse liver events are especially noteworthy as correlation to long-term clinical outcomes has not been established. In addition patients with complications of cirrhosis and hepatic decompensation were excluded from these clinical trials. A warning for adverse hepatic events is included in the labeling.[1] Recommendations also include dose adjustment in patients with moderate or severe hepatic impairment and a post-marketing trial confirming efficacy and safety in this population. Further data from long-term safety extension studies found similar rates of serious adverse events between treatment groups without any obvious trends or underlying pathology. Only 2 deaths occurred during the course of the clinical trials in patients takin obeticholic acid, both of which were thought to be unrelated to study treatment.[1]

Pharmacology and Pharmacokinetic Properties:[3]

Parameter	
Mechanism of Action	Obeticholic acid is an agonist at the farnesoid X receptor, a nuclear receptor located in liver and intestinal cells. Activation of this receptor results in decreased levels of bile via suppression of bile production from *de novo* cholesterol synthesis and increased biliary transport out of the liver.
Absorption	T_{max}: parent drug = 1.5 hours; active metabolites = 10 hours Food has no effect on bioavailability
Distribution and Protein Binding	Protein binding >99% V_d=618 liters
Metabolism	Conjugation with glycine or taurine in the liver to form active metabolites which undergo enterohepatic circulation.
Elimination	87% feces <3% urine

Abbreviations: T_{max}=time to maximal concentration, V_d=volume of distribution

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Mortality
2) Liver disease progression (fibrosis) or time to liver failure
3) Complications of cirrhosis (liver transplant, hospitalizations, hepatic encephalopathy, hepatorenal syndrome)
4) Health-related quality of life
5) Early discontinuation due to adverse events
6) Serious adverse events

Primary Study Endpoint:
1) "Response" to treatment defined as: ALP < 1.67-times ULN; reduction of ALP ≥15% from baseline; AND total bilirubin level within normal limits.

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. Nevens, et al.[11] Phase 3, DB, PC, PG, RCT	1. OCA 10 mg daily 2. OCA 5 mg daily titrated to 10 mg daily at 6 months if lacking ADE with inadequate treatment response 3. PBO 1:1:1 12 months	Demographics: - Mean age: 56 years - Female: 91% - White: 94% - Ursodiol use: 93% - Mean ALP 323 units/L - Bilirubin <ULN: 92% Key Inclusion Criteria: - PBC diagnosis consistent with AASLD and EASL guidelines* - Adults ≥18 years of age - ALP ≥1.67x ULN or bilirubin >ULN - Baseline ursodiol therapy x12 months or intolerance to ursodiol (off ursodiol for ≥3 months) Key Exclusion Criteria: - H/o other liver disease - Bilirubin >2x ULN - Complications of cirrhosis or hepatic decompensation (MELD ≥15, awaiting transplant, portal hypertension, hepatorenal syndrome) - H/o severe pruritus - Concurrent fibrates, antibody therapy or immunosuppressants, other hepatotoxic medications - Prolonged QTc >500ms	ITT: 1. 73 2. 71 3. 73 mITT (all patients receiving at least 1 dose): 1. 73 2. 70 3. 73 Attrition: 1. 9 (12%) 2. 7 (10%) 3. 3 (4%)	Primary Endpoint: Response to treatment (ALP <1.67x ULN, ALP decrease >15%, and bilirubin ≤ULN) 1. 34 (47%); OR 9.4 (95% CI 3.7 to 23.9) vs. PBO 2. 32 (46%); OR 9.1 (95% CI 3.6 to 23.2) vs. PBO 3. 7 (10%); p<0.001 for both groups vs. PBO Secondary Endpoints at 12 months: Change in AST (units/L) 1. -14.0 (SD 99.3) LSMD -16.0 (SE 3.9) 2. -12.5 (SD 14.1) LSMD -14.1 (SE 3.8) 3. 3.0 (SD 31.7) p<0.001 for both groups vs. PBO Change in ALT (units/L) 1. -24.4 (SD 26.6) LSMD -20.4 (SE 3.1) 2. -22.3 (SD 21.2) LSMD -16.3 (SE 3.0) 3. -3.9 (SD 20.0) p<0.001 for both groups vs. PBO Change in ALP (units/L) 1. -117.7 (SD 73.3) LSMD -115.5 (SE 13.2) 2. -103.5 (SD 87.0) LSMD -98.1 (SE 13.1) 3. -7.7 (SD 88.0) p<0.001 for both groups vs. PBO	1. ARR: 37% NNT: 3 2. ARR: 36% NNT: 3 NA NA NA	Serious AE: 1. 8 (11%) 2. 11 (16%) 3. 3 (4%) p-value NR DC due to AE: 1. 8 (11%) 2. 4 (6%) 3. 2 (3%) p-value NR Pruritus 1. 50 (68%) 2. 39 (56%) 3. 28 (38%) p-value NR	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: LOW. Randomization via IWRS; stratified by risk criteria (ALP, AST, bilirubin levels) and ursodiol use. Balanced baseline characteristics. Performance Bias: LOW. Patient and investigators blinded via matching placebo. Blinding of assessors not stated. Use of objective laboratory outcomes minimizes bias. Detection Bias: LOW. Blinding of assessors was not stated, but use of objective laboratory outcomes minimizes risk of bias. Study appeared adequately powered for defined endpoint. Attrition Bias: LOW. Overall attrition was low, but was higher in treatment groups (10-12% vs. 4%). Data analyzed using mITT with missing data classified as non-responders giving a more conservative estimate of effect. Reporting Bias: LOW. All specified outcomes reported. Study was funded by Intercept who was involved in trial design, data collection, and writing the manuscript. Data management and statistical analysis performed by third-party. **Applicability**: Patient: moderate/ severe disease, decompensation or complications of cirrhosis were excluded. Majority of patients were white limiting applicability to other populations. Intervention: 93% of patients on ursodiol; 50% in group #2 increased to 10 mg at 6 months. Comparator: Placebo appropriate. Outcomes: Composite surrogate outcomes used to define treatment response. Individual components of the composite NR individually. Unclear if decrease of ALP observed (~100 units/L) would be associated with long-term outcomes. Minimum important changes in ALP has not been established for PBC. Setting: 59 sites in 13 countries from March 2012 to December 2013. 15 sites were in the

				Change in total bilirubin (mg/dL) 1. -0.07 (SD 0.25) LSMD -0.17 (SE 0.04) 2. -0.03 (SD 0.20) LSMD -0.13 (SE 0.04) 3. 0.08 (SD 0.24) P<0.001 for both groups vs. PBO	NA			United States but the exact percent of US patients was not reported.
2. Hirschfield, et al.[12] Phase 2, DB, PC, dose-response, RCT	1. OCA 10mg daily 2. OCA 25 mg daily 3. OCA 50 mg daily 4. Placebo 1:1:1:1 3 months Upon completion patients could enroll in an open-label extension study for up to 12 months	Demographics: - Female: 95% - White: 96% - Mean age: 55 years - Mean bilirubin 0.2 mg/dL - Mean ALP 287 units/L - Mean ursodiol dose 15.6-16.3 mg/kg/day Key Inclusion Criteria: - Age: 18-75 years - Diagnosis of PBC consistent with AASLD and EASL guidelines* - Stable dose of ursodiol for at least 6 months - ALP of 1.5-10x ULN Key Exclusion Criteria: - AST or ALT >5x ULN - Bilirubin >2x ULN - SCr > 1.5 mg/dL - H/o or presence of hepatic decompensation - Other liver diseases - Concurrent use of colchicine, methotrexate, azathioprine or systemic corticosteroids	ITT: 1. 38 2. 48 3. 41 4. 38 mITT (all patients who had a post-baseline ALP <7 days after last dose): 1. 38 2. 47 3. 39 4. 37 Attrition: 1. 6 (16%) 2. 6 (13%) 3. 16 (39%) 4. 1 (3%)	Primary Endpoint: Mean % change in ALP from baseline to 3 months 1. 24% (95% CI -30% to -18%) 2. 25% (95% CI -30% to -20%) 3. 21% (95% CI -30% to -12%) 4. 3% (95% CI -7% to 2%) RR not reported; p-value <0.0001 for all groups vs. PBO	NA	SAE: 1. 0 (0%) 2. 1 (2.1%) 3. 5 (12.2%) 4. 1 (2.6%) p-value NR DC due to AE: 1. 5 (13.2%) 2. 5 (10.4%) 3. 15 (36.6%) 4. 1 (2.6%) p-value NR Pruritus 1. 47% p=NS 2. 85% p<0.0003 3. 80% p<0.006 4. 50%	NA NA 1. NA 2. ARR: 0.35 NNH: 3 3. ARR: 0.30 NNH: 3	**Risk of Bias (low/high/unclear)**: Selection Bias: LOW. Computer randomization using a block size of 4 for each center. Allocation concealment was not stated. Performance Bias: LOW. Patients and providers blinded with use of matching placebo. Detection Bias: LOW. Blinding of assessors not stated. Use of objective laboratory outcomes limits risk of bias. Attrition Bias: HIGH. More patients in OCA groups discontinued treatment (13-39%) vs placebo (2.6%). P-values not reported. Missing values imputed using last observation carried forward which may overestimate treatment effect. Study appeared appropriately powered. Reporting Bias: HIGH. Funded by Intercept Pharmaceuticals who assisted with finalization of analysis, data presentation, and manuscript submission. **Applicability**: Patient: Inclusion of only patients with mild disease limits applicability to patients with moderate or severe disease. Limited inclusion of minority populations and male gender. Intervention: Patients maintained ursodiol therapy throughout trial. FDA approved dose was only studied in 38 patients. Comparator: Placebo appropriate to establish efficacy. Outcomes: Use of ALP as surrogate for response to treatment. Limited duration of 3 months may not capture full therapeutic effect. Effect on long-term clinical outcomes is unclear. Setting: 41 centers in North America and Europe from November 2007 to May 2009.

3. Neuschwander-Tetri, et al.[10] Phase 2, MC, PC, RCT	1. OCA 25 mg daily 2. Placebo 1:1 72 weeks with 24 weeks follow-up	Demographics: - Mean age: 51.5 years - HLD: 62.5% - HTN: 61% - DM: 53.5% - Definite NASH: 80% - Mean fibrosis stage: 1.9 - Stage 3 fibrosis: 22% - Mean NAFLD activity score: 5.2 Key Inclusion Criteria: - Histological evidence of definite or borderline NASH - Histological NAFLD total activity score ≥ 4 and ≥1 in individual categories Key Exclusion Criteria: - Cirrhosis or clinical evidence of hepatic decompensation - Other cause of liver disease - Alcohol consumption > 20 g/day for women or >30 g/day for men - Confounding conditions (Bile duct obstruction, PBC, ALT > 300 U/L, SCr >2 mg/dL, DM with A1C >9.5%, HIV, life expectancy <5 years, substance abuse)	ITT: 1. 141 2. 142 PP (included patients with a final biopsy): 1. 110 2. 109 Attrition: 1. 8 (7.3%) 2. 11 (10.1%)	Primary Endpoint: Improvement in liver histology (decrease in NAFLD activity score ≥2 without worsening of fibrosis) 1. 50 (45%) 2. 23 (21%) RR 2.2 (95% CI 1.4 to 3.3) p=0.0002 Secondary Endpoints: Resolution of NAFLD OR resolution of NASH with persistent NAFLD in patients w/definite NASH at baseline 1. 22 (22%) 2. 13 (13%) RR 1.7 (95% CI 0.9 to 3.2) p=0.08 Improvement in fibrosis score: 1. 36 (35%) 2. 19 (19%) RR 2.0 (95% CI 1.2 to 3.4) P=0.004	ARR: 24% NNT: 4 NA ARR: 16% NNT: 6	Serious AE: 1. 30 (27.3%) 2. 21 (19.3%) p-value NR DC due to AE: NR Mortality 1. 2 (1.8%) 2. 0 (0%) p-value NR Pruritus 1. 33 (23%) 2. 9 (6%) p<0.0001	NA NA NA ARR: 0.17 NNH: 6	**Risk of Bias (low/high/unclear)**: Selection Bias: LOW. Randomized centrally by computer generated procedure; stratified by site and diabetes status and blocked by date. Baseline characteristics generally balanced. Performance Bias: LOW. Use of matching placebo. Patients, investigators, clinical staff and pathologists were blinded. Detection Bias: LOW. Biopsies centrally assessed by blinded committee of pathologists that scored NAFLD activity, fibrosis stage and NASH. Attrition Bias: HIGH. Biopsy analysis d/c'd early because an interim analysis achieved superiority (64 patients did not have final biopsies and were excluded from the analysis). Overall attrition was similar between groups. Missing values imputed as non-responders providing a more conservative estimate of effect. Reporting Bias: LOW. Study funded by Intercept Pharmaceuticals and the National Institute of Diabetes, Digestive and Kidney Diseases. Intercept provided comments on the protocol but was not involved in the study design, analyses or publication. **Applicability**: Patient: Patients with hepatic decompensation were excluded. Mean fibrosis stage was 1.9. Intervention: Currently only 5 and 10 mg tablets are marketed. Comparator: Placebo appropriate to determine efficacy. Outcomes: NAFLD activity score has not been correlated with clinical outcomes and a minimum clinically important difference has not been determined. Limited duration trial with no data on long-term outcomes of cirrhosis. Setting: 8 sites in the USA from March 2011 to December 2012.

Abbreviations [alphabetical order]: AE = adverse effects; ALP = alkaline phosphatase; ALT = alanine aminotransferase; ARR = absolute risk reduction; AST = aspartate aminotransferase; CI = confidence interval; DC = discontinuation; DB = double-blind; DM = diabetes mellitus; HIV = human immunodeficiency virus; H/o = history of; IWRS = interactive web response system; ITT = intention to treat; LSMD = least squares mean difference; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NAFLD = non-alcoholic fatty liver disease; NASH = non-alcoholic steatohepatitis; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = not significant; OCA = obeticholic acid; PBC = primary biliary cirrhosis; PBO = placebo; PC = placebo-controlled; PG = parallel-group; QOL = quality of life; SAE = severe adverse effects; SCr = serum creatinine; SD = standard deviation; SE = standard error; ULN = upper limit of normal

*Diagnosis of PBC includes ≥2 of the following: increased ALP levels, positive antibody titers (anti-mitochondrial antibodies > 1:40 or PBC-specific antinuclear antibodies), or liver biopsy consistent with PBC.

References:

1. Obeticholic Acid Summary Review. US Food and Drug Administration Center for Drug Evaluation and Research. . http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/207999Orig1s000SumR.pdf. Accessed September 22, 2016.
2. Lindor KD, Gershwin ME, Poupon R, Kaplan M, Bergasa NV, Heathcote EJ. Primary biliary cirrhosis. *Hepatology.* 2009;50(1):291-308.
3. Ocaliva - obeticholic acid tablet, film coated [package insert]. New York, NY: Intercept Pharmacetuicals Inc; 2016.
4. Intercept. Intercept Receives Breakthrough Therapy Designation From FDA for Obeticholic Acid for Nonalcoholic Steatohepatitis (NASH) With Liver Fibrosis. http://ir.interceptpharma.com/releasedetail.cfm?ReleaseID=893699. Published January 2015; Accessed November 2016.
5. US Food and Drug Administration. Breakthrough Therapy. http://www.fda.gov/ForPatients/Approvals/Fast/ucm405397.htm. Accessed December 3, 2016.
6. Lee M. *Basic Skills in Interpreting Laboratory Data, 4th Ed.* Bethesda, MD: American Society of Health-system Pharmacists; 2009.
7. Institute for Clinical and Economic Review. Obeticholic Acid for the Treatment of Primary Biliary Cholangitis: Comparative Clinical Effectiveness, Value, and Value-Based Price Benchmarks. 2016.
8. Lammers WJ, van Buuren HR, Hirschfield GM, et al. Levels of alkaline phosphatase and bilirubin are surrogate end points of outcomes of patients with primary biliary cirrhosis: an international follow-up study. *Gastroenterology.* 2014;147(6):1338-1349 e1335; quiz e1315.
9. Institute for Clinical and Economic Review. Obeticholic Acid for the Treatment of Nonalcoholic Steatohepatitis: Comparative Clinical Effectiveness and Value. 2016.
10. Neuschwander-Tetri BA, Loomba R, Sanyal AJ, et al. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. *Lancet (London, England).* 2015;385(9972):956-965.
11. Nevens F, Andreone P, Mazzella G, et al. A Placebo-Controlled Trial of Obeticholic Acid in Primary Biliary Cholangitis. *N Engl J Med.* 2016;375(7):631-643.
12. Hirschfield GM, Mason A, Luketic V, et al. Efficacy of obeticholic acid in patients with primary biliary cirrhosis and inadequate response to ursodeoxycholic acid. *Gastroenterology.* 2015;148(4):751-761.e758.
13. Obeticholic Acid Medical Review. US Food and Drug Administration Center for Drug Evaluation and Research. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/207999Orig1s000MedR.pdf. Accessed Sepetmber 22, 2016.

OCALIVA- obeticholic acid tablet, film coated
Intercept Pharmaceuticals Inc

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

OCALIVA (obeticholic acid) tablets, for oral use
Initial U.S. Approval: 2016

INDICATIONS AND USAGE

OCALIVA, a farnesoid X receptor (FXR) agonist, is indicated for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA. This indication is approved under accelerated approval based on a reduction in alkaline phosphatase (ALP). An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1)

DOSAGE AND ADMINISTRATION

- Starting Dosage: The recommended starting dosage of OCALIVA is 5 mg orally once daily in adults who have not achieved an adequate response to an appropriate dosage of UDCA for at least 1 year or are intolerant to UDCA. (2.1)
- Dosage Titration: If adequate reduction in ALP and/or total bilirubin has not been achieved after 3 months of OCALIVA 5 mg once daily and the patient is tolerating OCALIVA, increase dosage to 10 mg once daily. (2.1)
- Maximum Dosage: 10 mg once daily (2.1, 5.1)
- Management of Patients with Intolerable Pruritus: See full prescribing information for management options. (2.2)
- Hepatic Impairment: See full prescribing information for dosage adjustment in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C). (2.3)

Administration Instructions

- Take with or without food. (2.4)
- For patients taking bile acid binding resins, take OCALIVA at least 4 hours before or 4 hours after taking a bile acid binding resin, or at as great an interval as possible. (2.4, 7.1)

DOSAGE FORMS AND STRENGTHS

Tablets: 5 mg, 10 mg (3)

CONTRAINDICATIONS

Patients with complete biliary obstruction (4)

WARNINGS AND PRECAUTIONS

- Liver-Related Adverse Reactions: Monitor for elevations in liver biochemical tests and development of liver-related adverse reactions; weigh the potential risk against the benefits of continuing treatment. Do not exceed 10 mg once daily. Adjust the dosage for patients with moderate or severe hepatic impairment. Discontinue in patients who develop complete biliary obstruction. (2.3, 4, 5.1)
- Severe Pruritus: Management strategies include the addition of bile acid binding resins or antihistamines; OCALIVA dosage reduction and/or temporary dosing interruption. (2.2, 5.2)
- Reduction in HDL-C: Monitor for changes in serum lipid levels during treatment. (5.3)

ADVERSE REACTIONS

Most common adverse reactions (≥ 5%) are: pruritus, fatigue, abdominal pain and discomfort, rash, oropharyngeal pain, dizziness, constipation, arthralgia, thyroid function abnormality, and eczema. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Intercept Pharmaceuticals at 1-844-782-ICPT or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

DRUG INTERACTIONS

- Warfarin: Potential for decreased INR; monitor INR and adjust the dosage of warfarin, as needed, to maintain the target INR range. (7.2)
- CYP1A2 Substrates with Narrow Therapeutic Index (e.g., theophylline and tizanidine): Potential for increased exposure to CYP1A2 substrates; monitor drug concentrations of CYP1A2 substrates with narrow therapeutic index. (7.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 5/2016

Obeticholic Acid (Ocaliva®)

Goal(s):

- Encourage use of ursodiol or ursodeoxycholic acid which has demonstrated decrease disease progression and increase time to transplantation.
- Restrict use to populations for which obeticholic acid has demonstrated efficacy.

Length of Authorization:

Up to 12 months

Requires PA:

- Obeticholic acid

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is this request for continuation of therapy previously approved by the FFS program (patient has already been on obeticholic acid)	**Yes:** Go to Renewal Criteria	**No:** Go to #3
3. Is the treatment for primary biliary cholangitis?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Does the patient have evidence of complications from cirrhosis or hepatic decompensation (e.g., MELD score ≥15; awaiting transplant; portal hypertension; or hepatorenal syndrome)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #5

Approval Criteria		
5. Is the total bilirubin level >2-times the upper limit of normal (ULN)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #6
6. Does patient have a documented intolerance or contraindication to ursodiol?	**Yes:** Document symptoms of intolerance or contraindication and approve for up to 12 months	**No:** Go to #7
7. Has patient had a 12-month trial of ursodiol with inadequate response to therapy (ALP ≥1.67-times the ULN or total bilirubin greater than the ULN)?	**Yes**: Document baseline ALP and total bilirubin level and appprove for up to 12 months ALP:_____ units/L Total Bilirubin _____ mg/dL	**No**: Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there evidence of improvement of primary biliary cholangitis, defined as: a. ALP <1.67-times the ULN; AND b. Decrease of ALP >15% from baseline: AND c. Normal total bilirubin level?	**Yes**: Document ALP and total bilirubin level and approve for up to 12 months ALP:_____ units/L Total Bilirubin _____ mg/dL	**No**: Pass to RPh. Deny; medical appropriateness

P&T / DUR Review: *01/17*
Implementation: *TBD*

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

New Drug Evaluation: lixisenatide injection, subcutaneous

Date of Review: January 2017
Generic Name: lixisenatide
PDL Class: GLP-1 receptor agonists

End Date of Literature Search: October 2016
Brand Name (Manufacturer): Adlyxin (Sanofi-Aventis)
AMCP Dossier Received: Yes

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

Research Questions:

- Is there comparative efficacy evidence that lixisenatide improves outcomes versus other GLP-1 receptor agonists in patients with type 2 diabetes mellitus (T2DM), including hemoglobin A1c (A1C) reduction, microvascular and macrovascular outcomes and mortality?
- Is there evidence that lixisenatide is safer than other GLP-1 receptor agonists in patients with T2DM?
- Are there subpopulations of patients, such as those with Medicaid coverage, with T2DM for which lixisenatide may be more effective or associated with less harm than alternative treatments?

Conclusions:

- Lixisenatide approval was based on 11 phase 3 clinical trials.[1-2] Eight trials were placebo-controlled and 3 were active treatment comparisons to either sitagliptin, exenatide or insulin glulisine. All trials were designed and funded by the manufacture Sanofi-Aventis. Limitations to the data include short trial durations (12-26 weeks for most) and insufficient evidence for improved health outcomes. Majority of patients enrolled in the studies had moderately uncontrolled T2DM (HbA1c around 8%) with few comorbidities. Analysis of the literature shows that lixisenatide lowers A1c < 1% and is associated with a modest weight loss of up to 1.3 kg (2.9 pounds). There is insufficient evidence to suggest lixisenatide is superior to currently available anti-diabetic treatments.
- There is insufficient evidence to determine if lixisenatide has any effect on microvascular outcomes.
- One study provides moderate quality evidence that lixisenatide is not associated with increased risk for macrovascular outcomes compared to placebo. Occurrence of the composite endpoint of cardiovascular mortality, nonfatal myocardial infarction (MI), nonfatal stroke, or hospitalization for unstable angina was 13.4% in the lixisenatide group and 13.2% in the placebo group (HR 1.02; 95% CI, 0.89 to 1.17).[11] Most events were nonfatal MIs (61.9% in the placebo group and 62.8% in the lixisenatide group). A predefined secondary endpoint of all-cause mortality found no statistically significant difference between lixisenatide and placebo (7.0% and 7.4%, respectively; p=0.50).
- There is moderate quality evidence that lixisenatide lowered A1c by -0.3% to -0.75% more than placebo as monotherapy, in combination with metformin, or in combination with metformin and basal insulin, sulfonylurea, or thiazolidinedione in patients with a mean age of 56 years and baseline A1c of 8.1%.[1-7] The

number of patients who obtained an A1c less than 7% was more common in patients treated with lixisenatide than placebo (number-needed-to-treat [NNT] of 4-6).[1-7]

- In patients with moderately uncontrolled T2DM (mean A1c of 8.02%) and 7-year history of a diabetes, lixisenatide was noninferior to exenatide at lowering A1c based on moderate quality evidence.[8] Hemoglobin A1c decreased -0.79% with lixisenatide compared to -0.96% with exenatide (LSMD 0.17%; 95% CI, -0.033 to 0.297%). All patients were on metformin. A similar number of patients in each group obtained an A1c less than 7%.[8]
- There is low quality evidence lixisenatide is noninferior to the rapid-acting insulin glulisine (with background insulin glargine ± metformin in both groups) at reducing A1c in patients with a 12-year history of T2DM and moderately uncontrolled glucose (mean A1c 8.5%).[10] Lixisenatide and insulin glulisine given once daily both resulted in A1c lowering of -0.6% compared to -0.8% for insulin glulisine given three times a day. The difference between lixisenatide and insulin glulisine once daily was -0.1% (95% CI, -0.17 to 0.06%) and -0.2% (95% CI, 0.10 to 0.33%) for lixisenatide compared to three times daily insulin glulisine. The number of patients obtaining an A1c less than 7% were similar for lixisenatide and once daily insulin glulisine compared to three times daily insulin glulisine (42.1%, 38.4% and 49.2%, respectively).[10]
- Common adverse events seen with GLP-1 receptor agonists (GLP-1 RAs) are gastrointestinal (GI) events, most notably vomiting, nausea and diarrhea. Pooled data from trials comparing lixisenatide to placebo demonstrated a 22% increased incidence of adverse GI events in patients treated with lixisenatide, leading to discontinuation in 4.3% of patients taking lixisenatide versus 0.5% of patients treated with placebo.[3]
- The glucose-dependent mechanism of action of lixisenatide lends itself to a low incidence of hypoglycemia. Lixisenatide had a 2-25% higher incidence of hypoglycemia compared to placebo; however, risk was highly dependent upon background therapy with the greatest risk in patients also taking a sulfonylurea (SU) or insulin.[12] Symptomatic hypoglycemia was defined as symptoms of hypoglycemia and a glucose level less than 60 mg/dL or prompt recovery after glucose or carbohydrate administration.[1-11]
- Withdrawal rates due to adverse events are an important assessment of tolerability. In all studies lixisenatide had higher early withdrawal rates due to adverse events. In placebo-controlled comparisons, lixisenatide was associated with approximately 10% of early withdrawals due to adverse events compared to 7% with placebo.[1-7] In active treatment comparisons, the average early withdrawal rate for lixisenatide was 6% versus 4% with comparators.[8-10]

Recommendations:

- Designate lixisenatide non-preferred and subject to current clinical prior authorization (PA) criteria for GLP-1 receptor agonists (See **Appendix 3**).

Background:

GLP-1 RAs are a class of antidiabetic treatments approved for subcutaneous use in patients with T2DM to lower HbA1c. GLP-1 RAs work by glucose-dependent insulin secretion and prevention of glucagon release. The mechanism of action of GLP-1 analogs result in reduced postprandial glucose (PPG) levels and reduced GI motility.[12] There are 5 GLP-1 RAs approved by the FDA: albiglutide, exenatide (including an extended-release formulation), dulaglutide, liraglutide and lixisenatide.[4] The extended-release formulation of exenatide, albiglutide, and dulaglutide are administered once weekly; exenatide is administered twice daily; and all other GLP-1 RAs are administered once a day. In addition to glucose-lowering effects, GLP-1 RAs are associated with modest weight loss, low risk of hypoglycemia, and small changes in blood pressure. GLP-1 RAs have also shown to decrease post-prandial glucose (PPG) levels; however, clinical significance of targeting PPG specifically has yet to be shown to result in improved health outcomes.[13] The adverse events most associated with GLP-1 RAs are GI-related (nausea, vomiting and diarrhea) which most commonly occur within the first 3-4 weeks of therapy. Dose titration of the GLP-1 RAs is recommended over a 2-4 weeks to minimize this effect.[5] Rare but serious adverse events associated with GLP-1 RAs are increased risk of pancreatitis, bile duct and gallbladder disease, and medullary thyroid carcinoma which has been observed in rodent models.[14]

Clinical practice guidelines recommend a goal A1c of less than 7% for most patients with T2DM, but goals of less than 6.5% or less than 8% may be reasonable depending on patient-specific factors, such as concomitant comorbidities and age.[6,7] Important clinical outcomes in patients with diabetes are microvascular and macrovascular complications, mortality, and serious adverse events (SAE) including symptomatic hypoglycemia. Hemoglobin A1c is used as a marker to assess comparative efficacy of different diabetes agents in clinical trials, and is associated with improved microvascular complications and possibly macrovascular outcomes as well.[15,16] Available data for most newer diabetes drugs are limited to short-term studies, which prevents the assessment of the durability of glucose lowering effects long-term and prevents comparison of impact on microvascular and macrovascular complications.

The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) guidelines recommend either a GLP-1 RA, sodium-glucose transporter-2 (SGLT-2) inhibitor, dipeptidyl peptidase-4 (DPP-4) inhibitor, α-glucosidase inhibitor, sulfonylurea (SU) or thiazolidinedione (TZD) as an option for patients who have hyperglycemia despite maximally tolerated metformin therapy.[15,16] An updated position statement by the American Diabetes Association (ADA) also suggests a role for GLP-1 RAs in patients on basal insulin that require additional glucose lowering.[15] However, the National Institute for Health and Care Excellence (NICE) recommends GLP-1 RAs as a third-line option in addition to metformin and a SU.[8] The Oregon Health & Science University Drug Effectiveness Review Project (DERP) found glucose lowering and incidence of GI events were similar between the GLP-1 RAs.[13]

Lixisenatide in the most recently approved GLP-1 RA in the United States, which follows the European approval in 2013.[5] The focus of this review is to evaluate the evidence related to the approval of lixisenatide and to provide recommendations for the Oregon Health Plan (OHP) fee-for-service Preferred Drug List (PDL) and recommendations for clinical prior authorization (PA) criteria, if appropriate.

See **Appendix 2** for **Highlights of Prescribing Information** from the manufacturer, including Black Boxed Warning and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Lixisenatide is given as a 20 mcg subcutaneous injection one hour before the first meal of the day.[12] Lixisenatide should be initiated at 10 mcg for 2 weeks and then titrated to 20 mcg if tolerated. Efficacy and safety data for lixisenatide are available from 14 clinical trials. Eleven trials have been published and are discussed below. Three trials were not applicable to the OHP population due to being studied exclusively in Asian countries and were therefore not included. The primary endpoint in all but two trials was change in A1c from baseline with secondary endpoints that included changes in body weight and number of patients who obtained an A1c less than 7%.[1-8,10] One trial assessed a composite primary endpoint of 2 unrelated outcomes: the percent of patients who obtained an A1c less than 7% and weight loss of at least 5%.[9] Another trial was a cardiovascular (CV) study which analyzed the composite endpoint of death from CV causes, nonfatal MI, nonfatal stroke or hospitalization for unstable angina.[11]

Placebo-controlled Trials
Fonseca, et al.[1]
In a 12-week, double-blind, placebo-controlled trial, 361 patients were randomized to once daily subcutaneous lixisenatide 2-step (10 mcg for one week, 15 mcg for one week, then 20 mcg), lixisenatide 1-step (10 mcg for 2 weeks then 20 mcg) or placebo 2-step or placebo 1-step (results combined).[1] Included patients were treatment-naïve with T2DM, baseline A1c of 8.04%, mean age of 54 years and 52% were males. Lixisenatide 2-step reduced A1c by 0.73%, lixisenatide 1-step by 0.85% and placebo by 0.19%. Both lixisenatide treatments were statistically superior to placebo in terms of A1c reduction compared to placebo, with a difference of -0.54% for lixisenatide 2-step and -0.66% for lixisenatide 1-step ($p<0.0001$ for both, no CI provided).[1] The number of patients who obtained an A1c

less than 7% was 52% with lixisenatide 2-step, 47% with lixisenatide 1-step and 27% for placebo (p<0.01 for both vs. placebo). All groups experienced weight loss with a mean change of 2 kg. Study limitations include the short study duration, the use in patients that were treatment-naïve (metformin is recommended first line by guidelines), the lack of complete statistical analyses (i.e., confidence intervals) and lack of detail on blinding methods which can all introduce biases into the study.

Riddle, et al.[2]
Lixisenatide was studied in a 24-week, randomized, double-blind, phase 3 study in patients with T2DM taking metformin with or without a SU, TZD and/or repaglinide.[2] Patients had a 9.2-year history of diabetes, mean A1c of 7.6%, were 56 years of age and predominately white (74%). After discontinuation of other antidiabetic agents other than metformin, a 12-week run-in period was used to add insulin glargine to patients' regimens. Insulin glargine doses were titrated weekly to a fasting range of 80-100 mg/dL. If after initial titration of insulin glargine during the run-in period the A1c remained greater than or equal to 7% but less than or equal to 9%, those patients were randomized to lixisenatide 20 mcg or placebo. Both groups were on background metformin and insulin glargine.[2] Patients in the lixisenatide group experienced a change in A1c of -0.7% compared to -0.4% in the placebo group (least square mean difference [LSMD] -0.3%; 95% CI, -0.5 to -0.2%; p<0.0001). The number of patients who obtained an A1c less than 7% was only modestly higher in the lixisenatide group compared to placebo (56% vs. 39%, respectively). There was a 0.3 kg weight gain in the lixisenatide group compared to a 1.2 kg weight gain in the placebo group. Applicability of this study is limited to patients already close to A1c goal. Other study limitations included the trial duration of only 24 weeks, lack of details on blinding of patients and practitioners and high attrition rates in the lixisenatide group compared to placebo (25% vs. 10%, respectively), which could bias results.[2]

Ahren, et al.[3]
Patients with elevated glucose levels despite optimal metformin therapy were randomized to subcutaneous lixisenatide 20 mcg in the morning, lixisenatide 20 mcg in the evening, placebo injection in the morning or placebo injection in the evening.[3] The study was a multicenter, double-blind trial of 680 patients with a history of T2DM for approximately 6 years. Included patients had moderately uncontrolled glucose levels indicated by a mean A1c of 8% while taking at least 1.5 g of metformin daily. Patients were a mean age of 55 years and obese (BMI 33 kg/m2). The primary endpoint was change in A1c at week 24 for lixisenatide given in the morning compared to placebo. Secondary endpoints were change in A1c in lixisenatide given in the evening compared to placebo, number of patients who obtained an A1c less than 7% and changes in weight. The study was not powered to directly compare the efficacy of lixisenatide given in the morning compared to the evening. Morning lixisenatide decreased A1c by 0.8%, evening lixisenatide decreased A1c by 0.9% and placebo decreased A1c by 0.4%.[3] The mean difference between morning lixisenatide and placebo was 0.5% (95% CI, -0.66 to -0.31%; p<0.0001) and the difference between evening lixisenatide and placebo was 0.4% (95% CI, -0.54 to -0.19%; p<0.0001).[3] The number of patients who obtained an A1c less than 7% was not statistically different between patients who received lixisenatide or placebo regardless of time of day of administration. Many details of the study design were lacking which introduces an unclear risk of bias and reduced confidence in the results.

Bolli, et al.[4]
In a 24-week, double-blind, placebo-controlled trial lixisenatide was compared to placebo in patients with T2DM and treated with metformin.[4] Patients were randomized to one of 4 groups: subcutaneous lixisenatide 2-step (10 mcg for one week, 15 mcg for one week, then 20 mcg), lixisenatide 1-step (10 mcg for 2 weeks then 20 mcg) or placebo 2-step or placebo 1-step (results combined). Included patients had a 6-year history of T2DM, mean A1c of 8%, were predominately white and were taking metformin 1.5 g/day for at least 3 months. Results were analyzed with a mITT analysis with LOCF used for handling missing data. At week 24, decreases in A1c were as follows: -0.8% for lixisenatide 2-step, -0.9% for lixisenatide 1-step and -0.4% for placebo (CI not provided; p<0.0001 for both placebo comparisons). More patients in the lixisenatide 1-step group obtained an A1c less than 7% compared to lixisenatide 2-step and placebo (47.4%, 42.1% and 24.2%, respectively).[4] Four patients would need to be treated with lixisenatide 1-step for 24 weeks to obtain this goal compared to 6 for lixisenatide

2-step. Changes in body weight were -2.6 kg for lixisenatide 2-step, -2.7 kg for lixisenatide 1-step and -1.6 kg loss for placebo (CI not provided; p<0.01 for both vs. placebo).[4] Randomization and blinding of outcome assessors was not described and could potentially bias results. Adding lixisenatide to metformin helped to get approximately 25% more patients to an A1c goal of less than 7%; however, over 50% of patients were still not able to obtain goal A1c with lixisenatide.

Rosenstock, et al.[5]
Patients with T2DM not controlled on a SU with or without metformin were randomized to lixisenatide 20 mcg or placebo for 24 weeks.[5] In this randomized, double-blind, phase 3 trial the mean age was 57 years, patients had a history diabetes for 9.4 years and a mean A1c of 8.3%. Patients with major comorbidities were excluded. Results were based on the mITT population (n = 822) with LOCF to account for missing data.[5] Lixisenatide lowered A1c by -0.85% and placebo lowered A1c by -0.10% (LSMD -0.74%; 95% CI, -0.867 to -0.621%; p<0.0001). More patients were able to obtain an A1c less than 7% with lixisenatide (36.4% vs. 13.5%, respectively). Lixisenatide use was shown to decrease weight more than placebo (LSMD -0.85 kg; 95% CI, -1.25 to -0.42; p<0.0001).[5] Many details on blinding and randomization were not described leading to a risk of selection, performance and detection bias.

Pinget, et al.[6]
Lixisenatide was studied in patients with moderately uncontrolled T2DM despite treatment with pioglitazone with or without metformin. In this phase 3, double-blind, multicenter trial, 484 patients were randomized to lixisenatide 20 mcg or placebo for 24 weeks with a variable extension option of at least 52 weeks.[6] Patients were a mean age of 56 years with moderately elevated glucose levels (A1c 8.1%). A majority of patients were obese (67.6%). The target dose of lixisenatide was 20 mcg after a 2-week dose titration phase. Results were analyzed in the mITT population using LOCF for missing data. Patients were on a median pioglitazone dose of 30 mg; 81% of patients were also taking metformin at a median daily dose of 2000 mg. Hemoglobin A1c was reduced by 0.9% with lixisenatide and reduced by 0.34% with placebo (LSMD 0.56%; 95% CI, -0.73 to -0.39%; p<0.0001).[6] There were more patients in the lixisenatide group that achieved an A1c of less than 7% (52.3% vs. 26.4%; NNT =4). Subgroup analysis on metformin use, race, gender, BMI and baseline A1c did not influence results. Changes in body weight were not statistically significant between groups (LSMD -0.41 kg; 95% CI, -1.03 to 0.20 kg; p=0.1864).[6] Details on blinding of providers and patients may introduce detection bias. Applicability of these results to non-white populations is limited.

Riddle, et al.[7]
Patients with a history of T2DM over 12 years were randomized to lixisenatide and placebo after failure to obtain glucose control with basal insulin with or without metformin.[7] The study was a 24-week, double-blind, phase 3 trial in 495 patients across multiple countries. Patients had at least a 3-month history of using insulin and metformin (if applicable), were mean age of 57 years, and had a baseline A1c of 8.4%. Use of basal insulin was predominately with insulin glargine (50%) or NPH (40%). Results were analyzed using mITT with LOCF for missing data. Lixisenatide lowered A1c by -0.7% compared to -0.4% in the placebo group (LSMD 0.4% (95% CI -0.6 to -0.2%; p=0.0002). Twenty-eight percent of the patients in the lixisenatide group obtained an A1c less than 7% compared to 12% in the placebo group (p<0.0001). Changes in weight were -1.8 kg for lixisenatide and -0.5 kg for placebo.[7] Extrapolation of results would be most appropriate in white patients who already on a basal insulin and metformin who are already close to achieving their A1c goal. Other limitations include short study duration and predominantly white population.

Active Treatment Comparisons
Rosenstock, et al.[8]
In a noninferiority trial, lixisenatide was compared to exenatide in patients taking metformin over 24 weeks.[8] The trial was open-label, parallel-group, phase 3 study in patients with a history of T2DM for approximately 7 years. Most patients were white (93%) with a mean age of 57 years and a baseline A1c of 8%. Lixisenatide was titrated over 2 weeks to a target dose of 20 mcg daily and exenatide was titrated over 4 weeks to a target dose of 10 mcg twice daily. Data were

analyzed in the mITT population with a noninferiority margin set at 0.4% for the upper limit of the 95% CI. Lixisenatide was found to be noninferior to exenatide at lowering A1c with no clinically significant difference in A1c lowering. Hemoglobin A1c reductions were -0.79% with lixisenatide and -0.96% for exenatide (LSMD 0.17%; 95% CI, -0.033 to 0.297%).[8] There were a similar number of patients who obtained an A1c less than 7% in each group (48.5% and 49.8%, respectively). Changes in weight were -2.96 kg for patients on lixisenatide and -3.98 kg for exenatide-treated patients.[8] The high percentage of white patients limits the applicability of the results to other races and ethnicities. The short trial duration limits the ability to determine long term differences between treatments. The open-label study design increases risk for detection and performance bias.

Van Gaal, et al.[9]
In a double-blind, 24-week, randomized trial, subcutaneous lixisenatide 20 mcg was compared to oral sitagliptin 100 mg in obese patients (n=319) less than 50 years of age with T2DM.[9] Patients had a mean baseline A1c of 8.1%, were mostly white (81%) with a mean age of 43 years and BMI of 36.8 mg/k^2. Patients had similar baseline characteristics except the lixisenatide group had 10% fewer males than the sitagliptin group. The data were analyzed using mITT design with LOCF for missing data. The primary composite endpoint was the number of patients who obtained an A1c less than 7% and weight loss of at least 5%, an interesting composite of 2 unrelated endpoints. The trial primary endpoint suggests targeting a population with a rising incidence of diabetes with associated obesity. Secondary endpoints were similar to the other studies. There was no statistically significant difference an achievement of goal A1c plus 5% weight loss between lixisenatide and sitagliptin (12% vs. 7.5%, respectively; LSMD 4.6%; 95% CI, -1.8 to 11.0%; p=0.1696).[9] The number of patients who obtained an A1c less than 7% was the same in both groups (40%); glucose lowering (-0.7%) was also about the same. Weight loss of 2.5 kg was observed in the lixisenatide group compared to weight loss of 1.2 kg in sitagliptin patients (p=0.0006). A 10% difference in gender between the groups could impact the results of such a small study. Additionally, lack of details on randomization and blinding allows for an unclear risk of bias. The results of this study are most likely to apply to younger obese T2DM patients.

Rosenstock, et al.[10]
In an open-label, noninferiority, phase 3 trial, lixisenatide was studied in uncontrolled T2DM patients taking once daily rapid-acting insulin glulisine or three times daily insulin glulisine in addition to insulin glargine with or without metformin.[10] Patients meeting inclusion criteria had at least a 12-year history of T2DM, mean A1c of 8.4% and a mean age of 60 years. Ninety percent were taking metformin in addition to a mean dose of 55 units/day of insulin glargine as background therapy. All other oral antidiabetic (OAD) therapies besides metformin were discontinued. After randomization, glargine doses were titrated weekly to achieve a fasting glucose of 80-100 mg/dL for the first 4 weeks. There were 3 co-primary endpoints: noninferiority of lixisenatide compared to glulisine once daily in A1c reduction; lixisenatide compared to glulisine three times daily for noninferiority in A1c reduction; or superiority of lixisenatide compared to glulisine three times daily in change in body weight. Lixisenatide and daily insulin glulisine lowered A1c by -0.6% and glulisine three times daily lowered A1c by -0.8%, which met the noninferiority margin for both. The highest number of patients who obtained an A1c less than 7% was in the three times daily glulisine group (49%), followed by lixisenatide-treated patients (42%) and the once daily glulisine group (38%). Patients in the lixisenatide group lost 0.6 kg of body weight compared to weight gains in the once daily and three times daily glulisine groups (1.0 kg and 1.4 kg, respectively); however, differences were not statistically significant.[10] The open-label study design introduces performance bias and the short trial duration limits the ability to assess clinically meaningful long-term efficacy and safety outcomes.

Cardiovascular Study
Pferrer, et al.[11]
Lixisenatide was studied in a double-blind, multicenter, placebo-controlled, randomized trial in patients with a history of T2DM and an acute coronary syndrome (ACS) diagnosis less than 180 days before time of screening.[11] Patients were randomized to lixisenatide (n=3031) or placebo (n=3032) injected subcutaneously for

a median of 25 months and background anti-diabetic treatments. Treatments for diabetes were adjusted according to local practice standards to obtain appropriate glucose control. Twenty-six percent of patients were seen in the US. Patients were on average 60 years of age with a 9-year or more history of T2DM, A1c of 7.7%, 69% male and 75% white. A majority (90%) of patients were on an additional diabetes medication, the most common being metformin (63%) and sulfonylureas (31%). A similar number of patients in each group were on background therapy at baseline. Eighty-five percent of patients were taking an angiotensin receptor blocker (ARB) or ACE inhibitor and 84% were also on a beta-blocker. Qualifying ACS events were non ST-elevation myocardial infarction (NSTEMI), ST-elevation myocardial infarction (STEMI), or unstable angina. The trial was event-driven with the primary analysis conducted in the ITT population. Noninferiority was determined if the upper boundary of the 95% confidence interval (CI) of the hazard ratio (HR) was less than 1.3 and superiority would be found if the upper boundary was less than 1.0. A HR of 1.3 indicates that there could be 30% more events in the lixisenatide group and till be considered noninferior to placebo. The primary endpoint was the composite of death from CV causes, nonfatal MI, nonfatal stroke or hospitalization from unstable angina. Key secondary endpoints were hospitalization for heart failure (HF) and death from any cause. Lixisenatide was found to be noninferior to placebo for the primary endpoint but not superior. Occurrence of the primary endpoint was 13.4% in the lixisenatide group and 13.2% in the placebo group (HR 1.02; 95% CI, 0.89 to 1.17).[11] The most common event type in both groups were nonfatal MI events (61.9% in the placebo group and 62.8% in the lixisenatide group). Rates of hospitalizations due to HF were similar between groups with an incidence of 4% in patients on lixisenatide and 4.2% of patients taking placebo (HR 0.96; 95% CI, 0.75 to 1.23; p=0.75). There was a 7.2% incidence of death in the placebo group compared to 7.0% in the lixisenatide group (p=0.50).[11] This study shows that in patients who meet the inclusion criteria, lixisenatide does not decrease risk of a cardiovascular events.

Clinical Safety:

Common adverse reactions associated with lixisenatide are presented in Table 1. Lixisenatide was associated with a higher incidence of adverse GI events, mostly mild to moderate, compared to placebo in pooled placebo-controlled trials, with 39.7% of patients in the lixisenatide group with an event compared to 18.4% in the placebo group.[12] Early discontinuation rates due to adverse GI events were 4.3% of patients in the lixisenatide groups compared to 0.5% in the placebo groups. Hypoglycemia associated with clinical symptoms, a glucose level less than 60 mg/dL or a quick recovery of symptoms after administration of a glucose or other carbohydrate was more common in lixisenatide treated-patients and occurred up to 25% more often than placebo-treated patients. Hypoglycemia risk was dependent on background therapies with the highest risk seen in patients also taking insulin or a SU, or when lixisenatide was given at night compared to the morning. Severe hypoglycemia, defined as clinical symptoms that require assistance from another person or a glucose level less than 36 mg/dL, rarely occurred.[1-12] Lixisenatide can be used in patients with moderate renal impairment (estimated creatinine clearance (CrCl) of 30 to less than 60 mL/min/1.73 m^2) but use in severe renal failure is not advised. Rare but serious adverse reactions include acute kidney injury or worsening of chronic renal failure, pancreatitis and risk for anaphylaxis. Antibody development to lixisenatide has been seen in 70% of patients involved in clinical trials with 2.4% having an attenuated response to treatment.[12] Antibodies to other GLP-1 receptor agonists have also been noted with higher levels in exenatide treated patients compared to liraglutide.[9] Long term data is needed to further define this risk.

Table 1. Adverse Reactions occurring in ≥5% of patients treated with lixisenatide[12]

Adverse Reaction	Placebo (n=1639)	Lixisenatide (n=2869)
Nausea	6%	25%
Vomiting	2%	10%
Headache	6%	9%
Diarrhea	6%	8%
Dizziness	4%	7%

Pharmacology and Pharmacokinetic Properties: Lixisenatide[12]

Parameter	
Mechanism of Action	GLP-1 RA which increases glucose-dependent insulin release, decreases glucagon secretion and slows gastric emptying
Absorption	1-3.5 hours when given subcutaneously
Distribution and Protein Binding	100 L
Metabolism	Glomerular filtration and proteolytic degradation
Half-Life	3 hours
Elimination	Glomerular filtration and proteolytic degradation

Abbreviations: RA – receptor antagonist

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:

1) Number of patients with an A1c <7%
2) Mortality
3) Macrovascular outcomes
4) Microvascular outcomes

Primary Study Endpoint:

1) Change in A1c from baseline
2) Composite endpoint of death from CV causes, nonfatal MI, nonfatal stroke or hospitalization from unstable angina
3) Composite endpoint of number of patients with an A1c less than 7% and weight loss of at least 5%

Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/N NH	Risk of Bias/ Applicability
Placebo-controlled Trials								
1. Fonseca, et al.[1] MC, PG, DB, PC, Phase 3 Sponsor: Sanofi-Aventis	1. Lixisenatide 2-step (L2)* 2. Lixisenatide 1-step (L1)^ 3. Placeboł Duration: 12 weeks * 10 mcg SC daily for 1 week, 15 mcg SC daily for 1 week, and then 20 mcg SC daily ^ 10 mcg SC daily for 2 weeks, then 20 mcg SC daily ł placebo 2-step and placebo 1-step results were combined (same dosing pattern as for lixisenatide 2-step and lixisenatide 1-step)	Demographics: Mean age: 54 yrs Males: 52% White: 72% Baseline A1c: 8.04% Duration of DM: 1.3 yrs. Key Inclusion Criteria: - Age 20-85 years - T2DM - Treatment naïve - A1c ≥7.0% to ≤10% Key Exclusion Criteria: - Prior use of an antidiabetic agent - FPG >250 mg/dL - Elevated pancreatic enzymes - GI disease - Pancreatitis - History of N/V - GI surgery - CVD - Hepatic disease - Renal disease	mITT: L2:120 L1: 119 P: 122 PP: L2: 110 L1: 108 P: 113 Attrition: L2: 8.3% L1: 9.2% P: 7.4%	Primary Endpoint: Change from baseline A1c: L2: -0.73% L1: -0.85% P: -0.19% L2 vs P: LSMD -0.54% (CI not reported) p<0.0001 L1 vs P: LSMD -0.66% (CI not reported) p<0.0001 Secondary Endpoints: Patients with A1c <7%: L2: 52% L1: 47% P: 27% P <0.01 for both comparisons to placebo Change in body weight: L2: -2 kg L1: -2 kg P: -2 kg	 NA NA 25%/4 20%/5 NS	Outcome: Serious AE: L2: 1 (0.83%) L1: 0 (0%) P: 5 (4.1%) (p-value not reported) D/C due to AE: L2: 5 (4.2%) L1: 3 (2.5%) P: 1 (0.8%) (p-value not reported) Gastrointestinal AE: L2: 39 (32.5%) L1: 38 (31.9%) P: 17 (13.9%) (p-value not reported) Symptomatic Hypoglycemia*: L2: 3 (2.5%) L1: 1 (0.8%) P: 2 (1.6%) (p-value not reported)	 NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) randomized using an interactive voice response system. Performance Bias: (unclear) double-blind design but details not provided. Volume and dose titration was open-label. Detection Bias: (low) independent data monitoring committee. Attrition Bias: (low) attrition was low in all groups. Use of mITT was appropriate. Reporting Bias: (low) pre-specified outcomes were appropriately reported. Study was sponsored by the manufacturer. **Applicability**: Patient: patients were treatment-naïve which is rare in T2DM in which metformin is universally recommended as first line. Intervention: appropriate use of lixisenatide because the study dose is the recommended approved dose to be used in clinical practice if tolerated. Comparator: placebo comparison appropriate in this population who were recently diagnosed and receiving diet and exercise counseling. Outcomes: more A1c lowering was seen in the L1 group but less patients achieved an A1c <7% most likely to a higher baseline A1c of 8.06% compared to 7.97% in the L2 group and 8.07% in the placebo group. Change in A1c from baseline is not an appropriate surrogate outcome of efficacy because it has not been linked to clinically relevant health outcomes. It must also be balanced with other outcomes like hypoglycemia rates and goal A1c. Long-term health outcomes would be helpful. Setting: sixty-nine centers and 12 countries. Number of US sites not specified.

2. Bolli, et al.[2] MC, PG, DB, PC, Phase 3 Sponsor: Sanofi-Aventis	1. Lixisenatide 2-step + metformin (L2)* 2. Lixisenatide 1-step + metformin (L1)^ 3. Placebo + metforminł Duration: 12 weeks * 10 mcg SC daily for 1 week, 15 mcg SC daily for 1 week, and then 20 mcg SC daily ^ 10 mcg SC daily for 2 weeks, then 20 mcg SC daily ł placebo 2-step and placebo 1-step results were combined (same dosing pattern as for lixisenatide 2-step and lixisenatide 1-step) Median duration: 24 weeks	Demographics: Mean age: 56 yrs Males: 45% White: 91% Baseline A1c: 8% Duration of T2DM: 6 yrs. Key Inclusion Criteria: - Age 24-79 years - T2DM ≥1 yr. - Metformin monotherapy 1.5 g/day for ≥3 mo. - A1c 7.0-10% Key Exclusion Criteria: - FPG >250 mg/dL - pancreatitis - GI surgery - IBS	Mitt: L2: 161 L1: 161 P2: 80 P1: 82 PP: L2: 144 L1: 147 P2: 78 P1: 73 Attrition: L2: 11% L1: 10% P2: 1% P1: 10%	Primary Endpoint: Change from baseline A1c: L2: -0.8% L1: -0.9% P: -0.4% L2 vs. P: LSMD -0.4 (95% CI, -0.6 to -0.2; p<0.0001) L1 vs. P: LSMD -0.5 (95% CI, -0.7 to -0.3; p<0.0001) Secondary Endpoints: Patients with A1c <7%: L2: 68 (42.1%) L1: 76 (47.4%) P: 39 (24.2%) L2 vs P: p=0.0005 L1 vs P: p<0.0001 Change in body weight: L2: -2.7 kg L1: -2.6 kg P: -1.6 kg L2 vs P: LSMD -1.1 kg (CI not provided) p<0.01 L1 vs P: LSMD -1.0 kg (CI not provided) p<0.01	NA NA 18%/6 23%/4 NA NA	Outcome: Serious AE: L2: 7 (4.3%) L1: 5 (3.1%) P: 4 (2.5%) (p-value not provided) D/C due to AE: L2: 13 (8.1%) L1: 9 (5.6%) P: 4 (2.5%) (p-value not reported) Gastrointestinal AE: L2: 76 (47.2%) L1: 67 (41.6%) P: 35 (2.1.9%) (p-value not reported) Symptomatic Hypoglycemia*: L2: 4 (2.5%) L1: 3 (1.9%) P: 1 (0.6%) (p-value not reported) Injection Site Reactions: L2: 7 (4.3%) L1: 7 (4.3%) P: 2 (1.3%) (p-value not reported)	NA NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (unclear) randomization not described. Performance Bias: (low) double-blind design with matching placebo. Volume and dose titration was open-label. Detection Bias: (unclear) no details were provided on blinding of outcome assessors. Attrition Bias: (low) there was a 10% difference in attrition between groups. mITT with LOCF was used which is an appropriate way to analyze this data. Reporting Bias: (low) pre-specified outcomes were appropriately reported. **Applicability**: Patient: patients randomized to the lixisenatide 1-step had better A1c lowering with less GI adverse events. Metformin dose was approximately 2 g/day in all groups at baseline. Intervention: appropriate use of lixisenatide because the study dose is the recommended approved dose to be used in clinical practice if tolerated. Comparator: placebo comparison (on background therapy) appropriate in this population. Outcomes: Change in A1C from baseline is not an appropriate surrogate outcome of efficacy because it has not been linked to clinically relevant health outcomes. It must also be balanced with other outcomes like hypoglycemia rates and goal A1c. Long-term health outcomes would be helpful. Setting: seventy-five centers and 15 countries. Number of US sites not specified.

3. Ahren, et al.[3] MC, PG, DB, PC, Phase 3 Sponsor: Sanofi-Aventis	1. Lixisenatide 20 mcg SC AM + metformin* (LAM) 2. Lixisenatide 20 mcg SC PM + metformin* (LPM) 3. Placebo SC AM + metformin (P)* 4. Placebo SC PM + metformin (P)* Median duration: 24 weeks * Placebo group results were combined	Demographics: Mean age: 55 yrs Males: 44% White: 89% Baseline A1c: 8.1% Duration of T2DM: 6.1 yrs. Key Inclusion Criteria: - T2DM - Metformin monotherapy ≥1.5 g/day for ≥3 mo. - A1c 7.0%-10% Key Exclusion Criteria: - FPG >250 mg/dL - GI surgery/GI disease - pancreatitis - antidiabetic treatments other than metformin within last 3 mo. - ketoacidosis	mITT: LAM: 255 LPM: 255 P: 170 PP: LAM: 233 LPM: 224 P: 158 Attrition: LAM: 8.6 % LPM: 12.2% P: 7.1%	Primary Endpoint: Change from baseline A1c in AM: LAM: -0.9% P: -0.4% LSMD -0.5% (95% CI, -0.66 to -0.31; p<0.0001 Secondary Endpoints: Change from baseline A1c in PM: LPM: -0.8% P: -0.4% LSMD -0.4% (95% CI, -0.54 to -0.19) p<0.0001 Patients with A1c <7%: LAM: (43%) LPM: (40.6%) P: 19 (22%) p<0.0001 for both Change in body weight: LAM: -2.0 kg LPM: -2.0 kg P: -1.6 kg p=NS	NA NA 21%/5 19%/5 NS	Outcome: Serious AE: LAM: 5 (2.0%) LPM: 8 (3.1%) P: 2 (1.2%) (p-value not provided) D/C due to AE: LAM: 18 (7.1%) LPM: 14 (5.5%) P: 2 (1.2%) (p-value not reported) Gastrointestinal AE: LAM: 93 (36.5%) LPM: 105 (41.2%) P: 44 (25.9%) (p-value not reported) Symptomatic Hypoglycemia*: LAM: 6 (2.4%) LPM: 13 (5.1%) P: 1 (0.6%) (p-value not reported) Injection Site Reactions: LAM: 17 (6.7%) LPM: 17 (6.7%) P: 6 (3.5%) (p-value not reported)	NA NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (high) randomization details not provided. Performance Bias: (unclear) double-blind design but details not provided. Detection Bias: (unclear) no details were provided on blinding of outcome assessors. Attrition Bias: (low) attrition low with less than a 10% difference between groups. mITT with LOCF was used to analyze data. Reporting Bias: (low) pre-specified outcomes were appropriately reported. **Applicability**: Patient: more patients in the placebo group were male, 48% compared to 42% in the lixisenatide group. Intervention: appropriate use of lixisenatide because the study dose is the recommended approved dose to be used in clinical practice if tolerated. Comparator: placebo comparison (on background therapy) appropriate in this population that has a history of diabetes requiring antidiabetic medication. Outcomes: Change in A1C from baseline is not an appropriate surrogate outcome of efficacy because it has not been linked to clinically relevant health outcomes. It must also be balanced with other outcomes like hypoglycemia rates and goal A1c. Long-term health outcomes would be helpful. Setting: one hundred thirty-three centers and 16 countries. US sites not specified.

4. Riddle, et al. [4] MC, PG, DB, PC, Phase 3 Sponsor: Sanofi-Aventis	1. Lixisenatide 20 mcg SC daily + insulin glargine and metformin (L) 2. Placebo SC daily + insulin glargine and metformin (P) Median duration: 24 weeks	Demographics: Mean age: 56 yrs Males: 50% White: 74% Baseline A1c: 7.6% Duration of DM: 9.2 yrs. Key Inclusion Criteria: - BMI >20 kg/m2 - T2DM ≥1 yr. - Metformin use for 3 months ± SU, Meglitinide and/or TZD - A1c ≥7.0% to ≤10% Key Exclusion Criteria: - Prior use of an antidiabetic agent other than SU, TZD or meglitinide last 3 months - Use of weight loss drugs if not at stable dose for ≥3 mo. - Hypoglycemia awareness - GI disease	Mitt: L:223 P: 223 PP: L: 194 P: 211 Attrition: L: 25% P: 10%	Primary Endpoint: Change from baseline A1c: L: -0.7% P: -0.4% LSMD -0.3 (95% CI, -0.5 to -0.2; p<0.0001 Secondary Endpoints: Patients with A1c <7%: L: 121 (56%) P: 85 (39%) p=0.0001 Change in body weight: L: 0.3 kg P: 1.2 kg LSMD -0.9 kg (95% CI, -1.4 to -0.4; p=0.0012	 NA 17%/6 NA	Outcome: Serious AE: L: 17 (7.6%) P: 10 (4.5%) (p-value not reported) D/C due to AE: L: 19 (8.5%) P: 8 (3.6%) (p-value not reported) Gastrointestinal AE: L: 89 (39.9%) P: 36 (16.1%) (p-value not reported) Symptomatic Hypoglycemia*: L: 50 (6.7%) P: 5 (2.2%) (p-value not reported) Injection Site Reactions: L: 15 (22.4%) P: 30 (13.3%) (p-value not reported)	 NA NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) centrally randomized 1:1 with an interactive voice response system. Performance Bias: (unclear) double-blind design but details not provided. Volume and dose titration was open-label. Detection Bias: (low) outcome assessors blinded to treatment allocation. Attrition Bias: (high) there was a 10% difference between groups in attrition rates. mITT with LOCF was used to analyze data which could overestimate the treatment effect since attrition levels were 15% different between groups. Reporting Bias: (low) pre-specified outcomes were appropriately reported. **Applicability**: Patient: population had high external validity except for low numbers of non-white participants. Higher number of discontinuations in the lixisenatide group suggests issues with tolerability. Intervention: appropriate use of lixisenatide because the study dose is the recommended approved dose to be used in clinical practice if tolerated. Comparator: placebo comparison (on background therapy) appropriate in this population that has a history of diabetes requiring antidiabetic medication. Outcomes: Change in A1C from baseline is not an appropriate surrogate outcome of efficacy because it has not been linked to clinically relevant health outcomes. It must also be balanced with other outcomes like hypoglycemia rates and goal A1c. Long-term health outcomes would be helpful. Setting: one hundred forty centers and 25 countries. Number of US sites not specified.

5. Rosenstock, et al.[5] MC, PG, DB, PC, Phase 3 Sponsor: Sanofi-Aventis	1. Lixisenatide 20 mcg SC daily + SU ± metformin (L) 2. Placebo SC daily + SU ± metformin (P) Median duration: 24 weeks	Demographics: Mean age: 57 yrs Males: 51% White: 52.2% Baseline A1c: 8.3% Duration of DM: 9.4 yrs. Key Inclusion Criteria: - 20-79 years - T2DM - SU ± metformin - A1c 7.0-10% Key Exclusion Criteria: - Prior use of an antidiabetic agent other than metformin or SU in the prior 3 months - FPG >250 mg/dL - CV disease - End-stage renal disease - GI disease - HTN - Elevated LFTs - Elevated pancreatic enzymes	mITT: L: 554 P: 274 PP: L: 499 P: 255 Attrition: L: 12.9% P: 10.8%	Primary Endpoint: Change from baseline A1c: L: -0.85% P: -0.10% LSMD -0.74% (95% CI, -0.867 to -0.621; p<0.0001) Secondary Endpoints: Patients with A1c <7%: L: 201 (36.4%) P: 38 (13.5%) p<0.0001 Change in body weight: L: -1.76 kg P: -0.93 kg LSMD -0.85 kg (95% CI, -1.25 to -0.42; p<0.0001)	NA 23%/4 NA	Outcome: Serious AE: L: 20 (3.5%) P: 16 (5.6%) (p-value not reported) D/C due to AE: L: 56 (9.8%) P: 14 (4.9%) (p-value not reported) Gastrointestinal AE: L: 235 (40.9%) P: 57 (20.0%) (p-value not reported) Symptomatic Hypoglycemia*: L: 88 (15.3%) P: 35 (12.3%) (p-value not reported) Injection Site Reactions: L: 26 (4.5%) P: 5 (1.8%) (p-value not reported)	NA NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (high) randomized in a 2:1. Details not provided. Performance Bias: (unclear) double-blind design but details not provided. Detection Bias: (unclear) no details were provided on blinding of outcome assessors. Attrition Bias: (low) attrition low with less than a 10% difference between groups. mITT with LOCF was used to analyze data is an appropriate considering the similar rates of attrition. Reporting Bias: (low) pre-specified outcomes were appropriately reported. **Applicability**: Patient: 84% were also taking metformin at time of randomization. Intervention: appropriate use of lixisenatide because the study dose is the recommended approved dose to be used in clinical practice if tolerated. Comparator: placebo comparison (on background therapy) appropriate in this population. Outcomes: Change in A1C from baseline is not an appropriate surrogate outcome of efficacy because it has not been linked to clinically relevant health outcomes. It must also be balanced with other outcomes like hypoglycemia rates and goal A1c. Long-term health outcomes would be helpful. Setting: one hundred thirty-six centers and 16 countries. Number of US sites not specified.

6. Pinget, et al.[6] MC, PG, DB, PC, Phase 3 Sponsor: Sanofi-Aventis	1. Lixisenatide 20 mcg SC daily + pioglitazone ± metformin (L) 2. Placebo SC daily + pioglitazone ± metformin (P) Median duration: 24 weeks	Demographics: Mean age: 57 yrs Males: 53% White: 84% Baseline A1c: 8.1% Duration of T2DM: 8.1 yrs. Key Inclusion Criteria: - Age ≥18 years - T2DM - Pioglitazone ≥30 mg/day ± metformin in previous 3 months - A1c ≥7.0% to ≤10% Key Exclusion Criteria: - Prior use of an antidiabetic agent other than pioglitazone or metformin in the prior 3 months - FPG >250 mg/dL - CV disease - End-stage renal disease - GI disease - pancreatitis - Elevated LFTs	mITT: L: 308 P: 148 PP: L: 288 P: 137 Attrition: L: 10.8% P: 14.9%	Primary Endpoint: Change from baseline A1c: L: -0.9% P: -0.34% LSMD -0.56% (95% CI, -0.73 to -0.39; p<0.0001 Secondary Endpoints: Patients with A1c <7%: L: 161 (52.3%) P: 39 (26.4%) p<0.0001 Change in body weight: L: -0.2 kg P: 0.2 kg LSMD -0.41 kg (95% CI, -1.03 to -0.20; p=0.1864	NA 26%/4 NS	Outcome: Serious AE: L: 8 (2.5%) P: 3 (1.9%) (p-value not reported) D/C due to AE: L: 21 (6.5%) P: 8 (5.0%) (p-value not reported) Gastrointestinal AE: L: 118 (36.5%) P: 46 (28.6%) (p-value not reported) Symptomatic Hypoglycemia*: L: 11 (3.4%) P: 2 (1.2%) (p-value not reported) Injection Site Reactions: L: 13 (4.0%) P: 7 (4.3%) (p-value not reported)	NA NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) randomized 2:1 by an interactive voice response system. Performance Bias: (unclear) double-blind design but details not provided. Detection Bias: (unclear) independent data monitoring committee. Blinding of assessors was not specified. Attrition Bias: (low) attrition low with less than a 10% difference between groups. mITT with LOCF was used to analyze data which is appropriate. Reporting Bias: (low) pre-specified outcomes were appropriately reported. **Applicability**: Patient: 81% were also taking metformin at time of randomization. Intervention: appropriate use of lixisenatide because the study dose is the recommended approved dose to be used in clinical practice if tolerated. Comparator: placebo comparison (on background therapy) appropriate in this population in this population that has a history of diabetes requiring antidiabetic medication. Outcomes: Change in A1C from baseline is not an appropriate surrogate outcome of efficacy because it has not been linked to clinically relevant health outcomes. It must also be balanced with other outcomes like hypoglycemia rates and goal A1c. Long-term health outcomes would be helpful. Setting: one hundred fifty centers and 13 countries. Almost half of study sites were in North America.

7. Riddle, et al.[7] MC, PG, DB, PC, Phase 3 Sponsor: Sanofi-Aventis	1. Lixisenatide 20 mcg SC daily + basal insulin therapy* (L) 2. Placebo SC daily + basal insulin therapy* (P) Median duration: 24 weeks * Metformin therapy was allowed if taking before enrollment	Demographics: -Mean age: 57 yrs -Males: 46% -White: 78% -Baseline A1c: 8.4% -Duration of DM: 12.5 yrs. Key Inclusion Criteria: -≥18 years -T2DM ≥1 year -Insulin ≥20 units/day for ≥3 months on stable dose -A1c 7.0%-10% -Stable metformin dose ≥1.5 g/day for ≥3 months Key Exclusion Criteria: -BMI ≤20.0 kg/m2 -Weight change >5.0 kg over 3 months -FPG >250 mg/dL -End-stage renal disease -pancreatitis -pregnancy	mITT: L: 327 P: 166 PP: L: 275 P: 147 Attrition: L: 16% P: 12%	Primary Endpoint: Change from baseline A1c: L: -0.7% P: -0.4% LSMD -0.4% (95% CI, -0.6 to -0.2; p=0.0002 Secondary Endpoints: Patients with A1c <7%: L: 86 (28%) P: 19 (12%) p<0.0001 Change in body weight: L: - 1.8 kg P: -0.5 kg LSMD -1.3 kg (95% CI, -1.8 to -0.7; p<0.0001	NA 16%/6 NA	Outcome: Serious AE: L: 12 (3.7%) P: 7 (4.2%) (p-value not reported) D/C due to AE: L: 25 (7.8%) P: 8 (4.8%) (p-value not reported) Gastrointestinal AE: L: 132 (40.2%) P: 34 (20.4%) (p-value not reported) Symptomatic Hypoglycemia*: L: 87 (26.5%) P: 35 (21.0%) (p-value not reported) Injection Site Reactions: L: 4 (1.2%) P: 1 (0.6%) (p-value not reported)	NA NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) centrally randomized 2:1 and allocated via an interactive voice response system. Performance Bias: (unclear) double-blind design but details not provided. Detection Bias: (low) investigators and data analysts unaware of study assignments. Attrition Bias: (low) attrition low with less than a 10% difference between groups. mITT with LOCF was used to analyze data. Reporting Bias: (low) pre-specified outcomes were appropriately reported. **Applicability**: Patient: patients has a mean basal insulin dose of 55 units/day and over 3-year history of insulin use at time of enrollment. Metformin use was 79% at baseline. Intervention: appropriate use of lixisenatide. Comparator: placebo comparison (on background therapy) appropriate in this population. Outcomes: Change in A1C from baseline is not an appropriate surrogate outcome of efficacy because it has not been linked to clinically relevant health outcomes. It must also be balanced with other outcomes like hypoglycemia rates and goal A1c. Long-term health outcomes would be helpful. Setting: one hundred and eleven centers and 15 countries.

Active Treatment Comparison Trials								
8. Rosenstock, et al.[8] MC, PG, OL, PC, Phase 3, noninferiority Sponsor: Sanofi-Aventis	1. Lixisenatide 20 mcg SC daily + metformin (L) 2. Exenatide 10 mcg SC twice daily + metformin (E) Median duration: 24 weeks	Demographics: Mean age: 57 yrs Males: 53% White: 93% Baseline A1c: 8.02% Duration of T2DM: 6.8 yrs. Key Inclusion Criteria: - Age 21-84 years - T2DM - Metformin ≥1.5 g/day in previous 3 months - A1c 7.0% to 10% Key Exclusion Criteria: - Prior use of an antidiabetic agent other than metformin in the prior 3 months - FPG >250 mg/dL - CV disease - End-stage renal disease - GI disease - pancreatitis - Elevated LFTs	mITT: L: 315 E: 315 PP: L: 277 E: 271 Attrition: L: 12.9% E: 14.2%	Primary Endpoint: Change from baseline A1c: L: -0.79% E: -0.96% LSMD 0.17% (95% CI, -0.033 to 0.297) (noninferiority met) Secondary Endpoints: Patients with A1c <7%: L: 152 (48.5%) E: 157 (49.8%) (p-value not reported) Change in body weight: L: -2.96 kg E: -3.98 kg LSMD 1.02 kg (95% CI, 0.456 to 1.581) (p-value not reported)	 NA NA NA	Outcome: Serious AE: L: 9 (2.8%) E: 7 (2.2%) (p-value not reported) D/C due to AE: L: 33 (10.4%) E: 41 (13%) (p-value not reported) Gastrointestinal AE: L: 137 (43.1%) E: 160 (50.6%) (p-value not reported) Symptomatic Hypoglycemia*: L: 8 (2.5%) E: 25 (7.9%) (p-value not reported)	 NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) randomized 1:1 by a centralized interactive voice response system. Performance Bias: (high) open-label study design. Detection Bias: (unclear) not described. Attrition Bias: (low) attrition low with less than a 10% difference between groups. mITT with LOCF was used to analyze data. Reporting Bias: (low) pre-specified outcomes were appropriately reported. **Applicability**: Patient: median metformin dose was 2,039 mg at baseline. There were 11% more males in the exenatide group compared to lixisenatide. Intervention: appropriate use of lixisenatide. Comparator: exenatide dose and titration according to manufacturer's recommendation. Outcomes: Change in A1C from baseline is not an appropriate surrogate outcome of efficacy because it has not been linked to clinically relevant health outcomes. It must also be balanced with other outcomes like hypoglycemia rates and goal A1c. Long-term health outcomes would be helpful. Setting: one hundred twenty-two centers and 18 countries. Almost half of study sites were in North America.

9. Van Gaal, et al.[9] MC, PG, DB, Phase 3 Sponsor: Sanofi-Aventis	1. Lixisenatide 20 mcg SC daily (L) 2. Sitagliptin 100 mg orally daily (S) Median duration: 24 weeks	Demographics: Mean age: 43 yrs Males: 40% White: 81% Baseline A1c: 8.1% Duration of T2DM: 4.4 yrs. Key Inclusion Criteria: - Age ≥18 and <50 years - T2DM ≥1 year - Metformin ≥1.5 g/day in previous 3 months - A1c ≥7.0% to ≤10% - BMI ≥30 kg/m2 Key Exclusion Criteria: - FPG >250 mg/dL - CV disease - GI surgery - Pancreatitis - Abnormal pancreatic enzymes - IBS - Diabetic ketoacidosis	mITT: L: 158 S: 161 PP: L: 142 S: 150 Attrition: L: 10.1% S: 6.8%	Primary Endpoint: Composite of proportion of patients obtaining an A1c <7% and body weight loss of ≥5%: L: 12.0% S: 7.5% MD 4.6% (95% CI, -1.8 to 11.0; p=0.1696 Secondary Endpoints: Patients with A1c <7%: L: 64 (40.7%) S: 64 (40.0%) MD 0.8% (95% CI, -9.7 to 11.3; p=0.884 Change from baseline A1c: L: -0.7% S: -0.7% LSMD 0.1% (95% CI, -0.2 to 0.3; p=0.6042 Change in body weight: L: -2.5 kg S: -1.2 kg LSMD -1.3 kg (95% CI, -2.1 to -0.6; p=0.0006	 NS NS NA NA	Outcome: Serious AE: L: 3 (1.9%) S: 3 (1.9%) (p-value not reported) D/C due to AE: L: 4 (2.5%) S: 5 (3.1%) (p-value not reported) Gastrointestinal AE: L: 48 (30.4%) E: 34 (21.1%) (p-value not reported) Symptomatic Hypoglycemia*: L: 1 (0.6%) S: 3 (1.9%) (p-value not reported)	 NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (unclear) no details provided. Performance Bias: (unclear) stated that it was double-blind and double-dummy but no other details were provided. Detection Bias: (unclear) not described. Attrition Bias: (low) attrition low with less than a 10% difference between groups. mITT with LOCF was used to analyze data. Reporting Bias: (low) pre-specified outcomes were appropriately reported. **Applicability**: Patient: a lower proportion of males by 10% were randomized to lixisenatide compared to sitagliptin. Patients on metformin to be included in study but metformin use during the study was not described. All patients were under 50 years and were obese (BMI 37 kg/m2). Intervention: appropriate use of lixisenatide. Comparator: sitagliptin dose appropriate. Outcomes: Difference in primary endpoints was driven by more weight loss in lixisenatide patients compared to sitagliptin. A1c lowering was the same. Change in A1C from baseline is not an appropriate surrogate outcome of efficacy because it has not been linked to clinically relevant health outcomes. It must also be balanced with other outcomes like hypoglycemia rates and goal A1c. Long-term health outcomes would be helpful. Setting: one hundred twenty-two centers and 18 countries. Almost half of study sites were in North America.

10. Rosenstock, et al.[10] MC, PG, OL, Phase 3, noninferiority Sponsor: Sanofi-Aventis	1. Lixisenatide 20 mcg SC daily + insulin glargine ± metformin (L) 2. Insulin glulisine 1-1X/day + insulin glargine ± metformin (GQD) 3. Insulin glulisine 1-3X/day + insulin glargine ± metformin (GTID) Median duration: 26 weeks	Demographics: Mean age: 60 yrs Males: 45% Baseline A1c: 8.5% Duration of T2DM: 12.2 yrs. Insulin use: 3.2 yrs. Key Inclusion Criteria: - Age >18 years - T2DM ≥1 year - ≥6 mo. basal insulin use ± 1-3 OADs - A1c 7.5-10.0% if on basal insulin or metformin; A1c 7.0-10.0% if on basal insulin an SU and/or a DPP-4 inhibitor and/or meglitinide - FPG ≤140 mg/dL - BMI >20.0-40.0 kg/m2 Key Exclusion Criteria: - pancreatitis - calcitonin >20 pg/mL - GI disease - Elevated LFTs - Elevated pancreatic enzymes	mITT: L: 297 GQD: 298 GTID: 295 PP: L: 268 GQD: 281 GTID: 285 Attrition: L: 10.1% GQD: 5.7% GTID: 4.0%	Primary Endpoint: Change from baseline A1c: L: -0.6% GQD: -0.6% GTID: -0.8% L vs. GQD: LSMD -0.1% (95% CI, -0.17 to 0.06) (noninferiority met) L vs. GTID: LSMD -0.2% (95% CI, 0.10 to 0.33) (noninferiority met) Secondary Endpoints: Patients with A1c <7%: L: 123 (42.1%) GQD: 112 (38.4%) GTID: 145 (49.2%) (p-value not reported) Change in body weight: L: -0.6 kg GQD: 1.0 kg GTID: 1.4 L vs. GQD LSMD -1.7 kg (95% CI, -2.26 to -1.06) (p-value not reported) L vs. GTID LSMD -2.0 (95% CI, 2.59 to 1.40; p<0.0001)	NA NA NA NA NA	Outcome: Serious AE: L: 11 (3.7%) GQD: 11 (3.7%) GTID: 14 (14.8) (p-value not reported) D/C due to AE: L: 15 (5%) GQD: 2 (0.7%) GTID: 3 (1.0%) (p-value not reported) Gastrointestinal AE: L: 105 (35.2%) GQD: 26 (8.6%) GTID: 22 (7.5%) (p-value not reported) Symptomatic Hypoglycemia*: L: 107 (35.9%) GQD: 140 (46.5%) GTID: 154 (52.4%) L vs. GQD: P =0.01 L vs. GTID: P=0.0001	NA NA NA NA 11%/9 17%/6	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) randomized 1:1 by interactive voice or web response system. Performance Bias: (high) open-label study design. Detection Bias: (unclear) no details were provided. Attrition Bias: (low) attrition low with less than a 10% difference between groups. MITT with LOCF was used to analyze data. Reporting Bias: (low) pre-specified outcomes were appropriately reported. **Applicability**: Patient: 90% were also taking metformin and glargine dose was 66 units/day at time of randomization. Most patients were obese with a long history of diabetes. Intervention: appropriate use of lixisenatide. Comparator: use of insulin glulisine is usually given three times daily with meals. Once daily dosing is not a common dosage frequency. Outcomes: Change in A1C from baseline is not an appropriate surrogate outcome of efficacy because it has not been linked to clinically relevant health outcomes. It must also be balanced with other outcomes like hypoglycemia rates and goal A1c. Long-term health outcomes would be helpful. Setting: one hundred ninety-nine centers and 18 countries. Number of US sites not specified.

Cardiovascular Study								
11. Pfeffer, et al.[11] MC, PG, DB, PC, Phase 3 Sponsor: Sanofi-Aventis	1. Lixisenatide 10 - 20 mcg SC daily (L) 2. Placebo SC daily (P) Median duration: 25 months	Demographics: Mean age: 60 yrs Males: 69.3% White: 75.2% Baseline A1c: 7.7% Duration of T2DM: 9.3 yrs. Qualifying ACS: STEMI (44%), non-STEMI (38.7%) and UA (17.2%) Key Inclusion Criteria: - ACS - T2DM Key Exclusion Criteria: - Age <30 yrs - PCI within 15 days - CABG - Coronary revascularization - eGFR < 30 mL/min per 1.73 m2 - A1c < 5.5 % or > 11%	ITT: L: 3034 P: 3034 PP: L: 2922 P: 2916 Attrition: L: 29% P: 25%	Primary Endpoint: Composite of death from CV causes, nonfatal MI, nonfatal stroke or hospitalization for UA: L: 406 (13.4%) P: 399 (13.2%) HR 1.02 (95% CI, 0.89 to 1.17; p=0.81) Secondary Endpoints: Hospitalization for HF: L: 122 (4.0%) P: 127 (4.2%) HR 0.96 (95% CI, 0.75 to 1.23; p=0.75) Death from any cause: L: 211 (7.0%) P: 223 (7.4%) HR 0.94 (95% CI, 0.78 to 1.13; p=0.50) Change in A1c: L: -0.6% P: -0.2% MD -0.27% (95% CI, -0.31 to -0.22; p<0.001)	 NS NS NS NA	Serious AE: L: 625 (20.6%) P: 699 (22.1%) (p-value not reported) D/C due to AE: L: 347 (11.4%) P: 217 (7.2%) p<0.001 Gastrointestinal AE: L: 149 (4.9%) P: 37 (1.2%) p<0.001 Hypoglycemia*: L: 504 (16.6%) P: 462 (15.2%) p=0.14	 NA 4%/25 4%/25 NS	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) randomized using a centralized assignment system. Performance Bias: (low) double-blind by matching SQ administration device and initial solution volume. Detection Bias: (low) outcomes were adjudicated by separate committees who were blinded to study assignment. Attrition Bias: (high) high rates of attrition in both groups (25-29%). mITT with LOCF was used to analyze data. Reporting Bias: (low) pre-specified outcomes were reported appropriately. Trial was funded by the manufacturer. **Applicability**: Patient: all patients had a recent history of ACS. 90% on concomitant diabetes medications (metformin, 64%; sulfonylurea, 31%). Patient socioeconomic status is unknown. Intervention: approved dose of lixisenatide dose used which allows applicability to Comparator: placebo comparison allows for determination that lixisenatide does not cause more cardiovascular harm than no treatment. Outcomes: composite of major cardiac events is an outcome required by the FDA to ensure new antidiabetic therapy is not associated with unacceptable levels of cardiac risk. Composite outcome driven by nonfatal MI events (61.9% in the placebo group and 62.8% in the lixisenatide group) Setting: forty-nine countries, 23% of patients were studied at US study sites.

Abbreviations [alphabetic al order]: A1C = hemoglobin A1C; ACS = acute coronary syndrome; AE = adverse events; ARR = absolute risk reduction; BMI = body mass index; CABG – coronary artery bypass graft; CI = confidence interval; CV = cardiovascular; CVD = cardiovascular disease; DB = double-blind; eGFR = estimated glomerular filtration rate; FBG = fasting blood glucose; GI = gastrointestinal; HF = heart failure; HR = hazard ratio; HTN = hypertension; IBS = inflammatory bowel disease; ITT = intention to treat; LFTs = liver function tests; LOCF = last observation carried forward; LSMD = least squares mean difference; MC = multi-center; MD = mean difference; MI = myocardial infarction; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; OAD = oral anti-diabetic agents; PC = placebo-controlled; PCI = percutaneous coronary intervention; PG = parallel group; PP = per protocol; SC = subcutaneous; STEMI = ST-segment elevation myocardial infarction; SU = sulfonylurea; T2DM = type 2 diabetes mellitus; TZD = thiazolinedinediones; UA = unstable angina.

* Symptomatic hypoglycemia defined as having symptoms consistent with hypoglycemia with a blood glucose <60 mg/dL or if no glucose measurement was done then prompt recovery after carbohydrate or glucose administration.

References:

1. Fonseca VA, Alvarado-Ruiz R, Raccah D, et al. Efficacy and safety of the once-daily GLP-1 receptor agonist lixisenatide in monotherapy: a randomized, double-blind, placebo-controlled trial in patients with type 2 diabetes (GetGoal-Mono). *Diabetes Care*. 2012;35(6):1225-1231. doi:10.2337/dc11-1935.

2. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. *N Engl J Med*. 2015;373(23):2247-2257. doi:10.1056/NEJMoa1509225.

3. Adlyxin [package insert]. Bridgewater, NJ. 2016.

4. Selph S, Blazine I, Guttmann-Bauman I. Drug Class Review Newer Diabetes Medications and Combinations. *Oregon Health and Science University, Portland, Oregon*. July 2016.

5. Handelsman Y, Mechanick JI, Blonde L, et al. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for developing a diabetes mellitus comprehensive care plan. *Endocr Pract*. 2011;17 Suppl 2:1-53.

6. Standards of medical care in diabetes--2015: summary of revisions. *Diabetes Care*. 2015;38 Suppl:S4. doi:10.2337/dc15-S003.

7. Garber AJ, Abrahamson MJ, Barzilay JI, et al. AACE/ACE comprehensive diabetes management algorithm 2015. *Endocr Pract*. 2015;21(4):438-447. doi:10.4158/EP15693.CS.

8. National Institute for Health and Care Excellence. Type 2 diabetes: lixisenatide. September 2013.

9. Nauck M. Incretin therapies: highlighting common features and differences in the modes of action of glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. *Diabetes Obes Metab*. 2016;18(3):203-216. doi:10.1111/dom.12591.

Appendix 1: Current Status on Preferred Drug List

GLP-1 RECEPTOR AGONISTS

ROUTE	FORMULATION	BRAND	GENERIC	PDL
SUB-CUT	PEN INJCTR	BYETTA	EXENATIDE	Y
SUB-CUT	PEN INJCTR	VICTOZA 3-PAK	LIRAGLUTIDE	N
SUB-CUT	VIAL	BYDUREON	EXENATIDE MICROSPHERES	N
SUB-CUT	PEN INJCTR	BYDUREON PEN	EXENATIDE MICROSPHERES	N
SUB-CUT	PEN INJCTR	TANZEUM	ALBIGLUTIDE	N
SUB-CUT	PEN INJCTR	TRULICITY	DULAGLUTIDE	N

Appendix 2: Highlights of Prescribing Information

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

ADLYXIN (lixisenatide) injection, for subcutaneous use
Initial U.S. Approval: 2016

----------INDICATIONS AND USAGE----------
ADLYXIN is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (1).

Limitations of Use (1):
- Has not been studied in patients with chronic pancreatitis or a history of unexplained pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.
- Not for treatment of type 1 diabetes or diabetic ketoacidosis.
- Has not been studied in combination with short acting insulin.
- Has not been studied in patients with gastroparesis and is not recommended in patients with gastroparesis.

----------DOSAGE AND ADMINISTRATION----------
- Initiate at 10 mcg once daily for 14 days. On Day 15, increase dosage to 20 mcg once daily (2.1).
- Administer once daily within one hour before the first meal of the day (2.2).
- Inject subcutaneously in the abdomen, thigh or upper arm (2.2).

----------DOSAGE FORMS AND STRENGTHS----------
- Injection: 50 mcg/mL in 3 mL in green prefilled pen (for 14 pre-set doses; 10 mcg per dose) (3).
- Injection: 100 mcg/mL in 3 mL in burgundy prefilled pen (for 14 pre-set doses; 20 mcg per dose) (3).

----------CONTRAINDICATIONS----------
Hypersensitivity to ADLYXIN or any product components. Hypersensitivity reactions including anaphylaxis have occurred with ADLYXIN (4).

----------WARNINGS AND PRECAUTIONS----------
- Anaphylaxis and Serious Hypersensitivity Reactions: Discontinue ADLYXIN and promptly seek medical advice (5.1).
- Pancreatitis: Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed. Consider other antidiabetic therapies in patients with a history of pancreatitis (5.2).
- Never share ADLYXIN pen between patients, even if the needle is changed (5.3).
- Hypoglycemia with Concomitant use of Sulfonylurea or Basal Insulin: When ADLYXIN is used with a sulfonylurea or basal insulin, consider lowering the dose of the sulfonylurea or basal insulin to reduce the risk of hypoglycemia. (5.4).
- Acute Kidney Injury: Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions. ADLYXIN is not recommended in patients with end stage renal disease (5.5).
- Immunogenicity: Patients may develop antibodies to lixisenatide. If there is worsening glycemic control or failure to achieve targeted glycemic control, significant injection site reactions or allergic reactions, alternative antidiabetic therapy should be considered (5.6).
- Macrovascular Outcomes: Clinical studies have not shown macrovascular risk reduction with ADLYXIN or any other antidiabetic drug (5.7).

----------ADVERSE REACTIONS----------
The most common adverse reactions (≥5%) of patients treated with ADLYXIN are nausea, vomiting, headache, diarrhea, dizziness, and hypoglycemia (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact sanofi-aventis at 1-800-633-1610 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- ADLYXIN delays gastric emptying which may impact absorption of concomitantly administered oral medications. Oral medications that are particularly dependent on threshold concentrations for efficacy, such as antibiotics, or medications for which a delay in effect is undesirable, such as acetaminophen, should be administered 1 hour before ADLYXIN (7.1, 12.3).
- Oral contraceptives should be taken at least 1 hour before ADLYXIN administration or 11 hours after the dose of ADLYXIN (7.1, 12.3).

----------USE IN SPECIFIC POPULATIONS----------
Pregnancy: ADLYXIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (8.1).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 7/2016

Glucagon-like Peptide-1 (GLP-1) Receptor Agonists

Goal(s):

- Promote cost-effective and safe step-therapy for management of type 2 diabetes mellitus (T2DM).

Length of Authorization:

- Up to 12 months

Requires PA:

- All GLP-1 receptor agonists

Covered Alternatives:

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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have a diagnosis of Type 2 diabetes mellitus?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA. • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class	**No:** Go to #4

Approval Criteria		
4. Has the patient tried and failed metformin and sulfonylurea therapy or have contraindications to these treatments? (document contraindication, if any)	**Yes: Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.

Initiating Metformin

1.	Begin with low-dose metformin (500 mg) taken once or twice per day with meals (breakfast and/or dinner) or 850 mg once per day.
2.	After 5-7 days, if gastrointestinal side effects have not occurred, advance dose to 850 mg, or two 500 mg tablets, twice per day (medication to be taken before breakfast and/or dinner).
3.	If gastrointestinal side effects appear with increasing doses, decrease to previous lower dose and try to advance the dose at a later time.
4.	The maximum effective dose can be up to 1,000 mg twice per day. Modestly greater effectiveness has been observed with doses up to about 2,500 mg/day. Gastrointestinal side effects may limit the dose that can be used.

Nathan, et al. Medical management of hyperglycemia in Type 2 Diabetes: a consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care*. 2008; 31;1-11.

P&T Review: *1/17 (KS); 11/16; 9/16; 9/15; 1/15; 9/14; 9/13; 4/12; 3/11*
Implementation: *2/15; 1/14*

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

New Drug Evaluation: **daclizumab** inj., subcutaneous

Date of Review: January 2017
Generic Name: daclizumab
PDL Class: Multiple Sclerosis

End Date of Literature Search: September 2016
Brand Name (Manufacturer): ZINBRYTA™ (Biogen Inc.)
AMCP Dossier Received: Yes

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

Research Questions:

- How does the efficacy of daclizumab compare with other systemic or biologic therapies for the treatment of relapsing forms of multiple sclerosis (RMS)?
- How does the safety of daclizumab compare with other systemic or biologic therapies for the treatment of RMS?
- Are there any specific subgroups based on demographics in which daclizumab is more efficacious or less harmful than other disease modifying agents for RMS?

Conclusions:

- One 96- to 144-week phase 3, randomized, active-controlled trial (DECIDE) and one 52-week phase 2, randomized, placebo-controlled trial (SELECT) provide moderate quality evidence daclizumab 105 mg subcutaneous (SC) every 4 weeks is superior to interferon beta-1a and placebo, respectively, at reducing the annualized relapse rate in patients with relapsing multiple sclerosis (RMS). For each trial, the daclizumab 150 mg group had a significantly lower annualized relapse rate than the interferon beta-1a group (0.22; 95% CI, 0.19-0.24 vs. 0.39; 95% CI, 0.35-0.44, respectively) and the placebo group (0.21; 95% CI, 0.16-0.29 vs. 0.46; 95% 0.37-0.57, respectively).
- Low quality evidence found the differences in patients who remained relapse-free during the phase 3 trial was 16% lower with the daclizumab 150 mg group versus interferon beta-1a control group but no statistical analysis of the difference was performed due to the hierarchical nature of the study design. Comparisons related to Expanded Disability Status Scores (EDSS) (range from 0 to 10, with higher scores indicating worse disability; mean EDSS score was 2.5 at baseline) were also not statistically different between groups based on low quality evidence.
- Adverse drug reactions (ADRs) of key interest for daclizumab include hepatotoxicity, cutaneous and other immune-mediated events, depression/suicide, malignancy, and death. In DECIDE, the daclizumab group, versus the interferon beta-1a group, had greater incidence of serious hepatotoxicity (0.7% vs. 0.4%), serious immune-mediated disorders (4% vs. <1%), immune-mediated disorders (32% vs. 12%), infection (65% vs. 57%), and depression/suicide (10% vs. 8%). In SELECT, the daclizumab group, versus the placebo group, had greater incidence of serious hepatotoxicity (1% vs. 0%), immune-mediated disorders (13% vs. 7%), infection (50% vs. 44%), and depression/suicide (7% vs. 2%). Some immune-mediated disorders resulted in serious patient harm, and one death occurred. Finally, daclizumab might increase the risk of breast cancer. Across all clinical studies, 0.5% of women and 0.1% of men treated with daclizumab developed breast cancer.

- Because of the serious risks associated with daclizumab, the U.S. Food and Drug Administration (FDA) requires drug labeling to carry black-boxed warnings for immune-mediated disorders, including autoimmune hepatitis, skin reactions, lymphadenopathy and non-infectious colitis.
- The full extent of ADRs is unclear because the short duration of the clinical trials relative to the chronic treatment of multiple sclerosis, and because subjects with history of malignancy, severe allergic reaction, recent serious infection, and abnormal laboratory results indicating significant disease were excluded from the trials. Persons of color were underrepresented, and older patients (age >55 years) and patients with greater disability (EDSS >5) were excluded from the trials. Therefore, no or limited data concerning the effectiveness and safety of daclizumab in these subpopulations are available.

Recommendations:

- Designate daclizumab as non-preferred and subject to clinical prior authorization criteria (see **Appendix 3**). Limit use to:
  - Adult patients with RMS; and
  - Without hepatic disease; and
  - Higher degree of ambulatory ability (EDSS ≤5); and
  - History of inadequate response to at least 2 disease modifying agents (DMA) approved for MS; and
  - Prescribed by a neurologists.

Background:

Daclizumab is indicated for adult patients with RMS and, because of its safety profile, should generally be reserved for patients with inadequate response to two or more drugs indicated for RMS.[1]

In the United States (U.S.), MS is the most common cause of neurological disability among young adults and affects an estimated 400,000 people. The median onset of MS is about 30 years of age and affects females more than males by a ratio of about 3:1.[2] Both direct and indirect costs rise continuously with each stepwise increase in disability as measured by the Expanded Disability Status Scale (EDSS).[3] In 2011 dollars, the estimated annual direct and indirect healthcare costs for patients with MS ranged from about $9000 to $55,000, with about 77% of total cost attributable to direct cost.[4]

The 3 major subtypes of MS are relapsing-remitting, secondary progressive, and primary progressive. About 85% of patients present with RRMS, which is marked by episodes of worsening or new neurological symptoms followed by periods of inactivity. Most patients with RRMS develop secondary progressive MS about 10 to 20 years after onset of disease, which is characterized by steady neurological decline with few or no clinically recognized relapses. About 15% of patients present with primary progressive MS, which is characterized by steady neurologic decline from onset for at least a year without distinct relapses.[5, 6, 7]

The course of MS is highly unpredictable and varies from person to person. About 15% of patients have a relatively benign course (EDSS≤4, duration >10 years), while about 60% to 70% develop secondary progression.[7, 8]

MS is managed by disease-modifying agents (DMA) and symptomatic and supportive therapies. Approved DMA include five forms of beta interferon, glatiramer acetate, natalizumab, teriflunomide, daclizumab, mitoxantrone, alemtuzumab, fingolimod, and dimethyl fumarate.[5, 9]

The goal of current MS therapy is to prevent relapse, disability progression, and brain and spinal cord injury. Accordingly, among the most important factors clinicians use to select a DMA in clinical practice are disease activity as measured by relapse rate, disability progression, and brain and spinal cord lesion burden on MRI, as well as a drug's potential to cause harm.[7]

In clinical trials, relapse rate most often serves as the primary efficacy endpoint, while disease progression as measured by change in EDSS score and lesion burden serve as secondary efficacy endpoints. The EDSS is based on the results of a neurological examination and the patient's ability to walk and is scored in 0.5 increments from 0 (normal neurological examination) to 10 (death from MS), with the value 5 corresponding to "ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (e.g., work a full day without special provisions)." [10, 11]

U.S. guidelines were developed in 2002 and republished in 2008 but have not been updated since the introduction of glatiramer acetate and interferon beta products.[5] Canadian 2013 evidence-based guidelines include newer DMAs but were developed before the introduction of teriflunomide, alemtuzumab, and daclizumab to Canada. These guidelines recommend glatiramer acetate or interferon beta-1b as the initial DMA of choice for RRMS patients; should a patient fail or have a contraindication to one, then the patient should be placed on the other. The guidelines further recommend dimethyl fumarate, fingolimod, and natalizumab for patients failing or having contraindications to both glatiramer acetate or interferon beta-1b. Combination therapy is not recommended.[12]

See **Appendix 2** for **Highlights of Prescribing Information** from the manufacturer, including Black Boxed Warning and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy: [13, 14, 15]
The FDA approval of daclizumab for the treatment of patients with RRMS is based on 2 randomized, double-blind, multicentered clinical trials:

- The DECIDE trial, a 96- to 144-week, phase 3 trial of daclizumab 150 mg subcutaneous (SC) every 4 weeks (n=919) vs. interferon beta-1a (Avonex) intramuscular (IM) 30 mcg once weekly (n=922)
- The SELECT trial, a 52-week, phase 2, dose-ranging study of daclizumab 150 mg (n=201) or 300 mg SC (not approved by FDA) every 4 weeks vs. placebo (n=196)

Both studies enrolled patients with RRMS 18 to 55 years of age and EDSS scores of 5 or less at baseline. The 2 studies differed in their criteria for the number of relapses required for enrollment (see Evidence Table). The primary endpoint for both studies was annualized adjusted relapse rate. For each trial, the daclizumab 150 mg group had a significantly lower annualized relapse rate than the interferon beta-1a group (0.22; 95% CI, 0.19-0.24 vs. 0.39; 95% CI, 0.35-0.44, respectively) and the placebo group (0.21; 95% CI, 0.16-0.29 vs. 0.46; 95% 0.37-0.57, respectively). The difference in the proportion of patients who were relapse-free between the daclizumab 150 mg was 16% lower versus interferon beta-1a. However, the difference was not statistically significant because the disability progression endpoint was ranked ahead of the relapse endpoint in the sequential closed testing model, and no significance was found for the disability comparison. Comparisons related to the MSIS-29 Physical Impact subscale were not significant for either study.

The studies had several validity concerns, particularly related to applicability of the results. Between the 2 studies, the number of patients in the U.S. was low (13% from U.S. and Canada for DECIDE and none for SELECT). Subjects were predominantly female (67%), white (92%), and young (mean age 36 years). Therefore, efficacy rates may be different for male, people of color, and older patients. Subjects had EDSS of 5 or less so the efficacy in patients with greater disability is unknown, which is likely to be the population more likely to receive this drug. Drug effectiveness remains unclear because the exclusion criteria in clinical trials were broad and subjective (e.g., subjects with history of malignancy, severe allergic reaction, recent serious infection, and significant medical condition in investigator's opinion). Lastly, MS is a chronic condition and most patients remain on a MS drug for their lifetime, so long-term safety and effectiveness outcomes are limited by the duration of the 2 studies. Daclizumab or matching placebo were administered in clinic for DECIDE, whereas

prescription is for self-administration, which may affect efficacy in practice. Patients already on an interferon preparation were included and not required to washout before randomization. Also, corticosteroids and glatiramer acetate treatment allowed up to within 30 days before randomization. Therefore, any continuing benefit from these therapies is a potential confounder. The studies do not address the best time to stop or to start the drug. Both studies had high attrition rates (21% daclizumab and 25% interferon in DECIDE; 18% daclizumab 150 mg, 19% daclizumab 300 mg, and 17% placebo in SELECT). Attrition was mostly driven by withdrawal of consent, adverse events, and perceived lack of efficacy. EDSS was assessed as a tertiary endpoint in SELECT. DECIDE has missing patient data for hyperintense lesions (14 patients in interferon group and 19 patients in daclizumab group) and Gd lesions (13 patients in interferon group and 19 patients in daclizumab group).

Clinical Safety:[1]

The most common adverse reactions from the DECIDE trial, with an incidence 2% or higher for the daclizumab 150 mg arm (n=919) than the interferon beta-1a arm (n=922) over a median length of treatment of about 27 months, were nasopharyngitis (25% vs. 21%), upper respiratory tract infection (URTI) (17% vs. 14%), rash (11% vs. 4%) influenza (9% vs. 6%), dermatitis (9% vs. 2%), oropharyngeal pain (8% vs. 4%), bronchitis (7% vs. 5%), eczema (5% vs. 2%), lymphadenopathy (5% vs. <1%), tonsillitis (4% vs. 2%), and acne (3% vs. <1%). The most common adverse reactions from the SELECT trial, with an incidence 2% or higher for the daclizumab 150 mg arm (n=208) than the placebo arm (n=204) over a median length of treatment of about 11 months, were URTI (9% vs. 7%), depression (7% vs. 2%), rash 7% vs. 3%), pharyngitis (6% vs. 4%), increased alanine aminotransferase (ALT) (5% vs. 2%), rhinitis (4% vs. 1%), as well as anemia, pyrexia, increased aspartate aminotransferase (AST), and dermatitis (3% vs. <1% each).

Due to the risk of immune-mediated disorders accompanying the use of daclizumab, the drug is only available through a Risk Evaluation and Mitigation Strategy (REMS) program that includes prescriber certification (enrollment and training), pharmacy certification, and patient enrollment and compliance with monitoring requirements.

An FDA Boxed Warning states daclizumab can cause severe and life-threatening hepatic injury, including autoimmune hepatitis and liver failure that may result in death. Across both clinical studies, 0.3% of daclizumab-treated patients experienced autoimmune hepatitis (with one case of death) and 1% experienced serious hepatotoxicity. In the DECIDE trial, serious hepatotoxicity occurred in 0.7% of the daclizumab group versus 0.4% of the interferon beta-1a; and in the SELECT trial, serious hepatotoxicity occurred in 1% of the daclizumab group versus none in the placebo group. Patients who received daclizumab had a greater incidence of ALT or AST elevations greater than 5-times the upper limit of normal (ULN) than those who received interferon beta-1a in the DECIDE trial (6% vs. 3%, respectively) or placebo in the SELECT trial (4% vs. 1%, respectively).

Because of the hepatotoxicity risk, daclizumab is contraindicated in patients who have a history or evidence of hepatic impairment or disease; liver function tests (LFTs) should be performed before and during therapy; and caution should be exercised with those also taking potentially hepatotoxic products.

The FDA Boxed Warning also indicates daclizumab increases the risk of immune-mediated disorders, including skin reactions, lymphadenopathy, and non-infectious colitis. Immune-mediated disorders were experienced by 32% in the daclizumab group versus 12% of the interferon beta-1a group in the DECIDE trial and 13% of the daclizumab group versus 7% of the placebo group in the SELECT trial. Serious immune-mediated disorders were experienced by 4% of the daclizumab group versus less than 1% of the interferon beta-1a group in the DECIDE trial and 0.5% in both the daclizumab and placebo groups in the SELECT trial. Some immune-mediated disorders did not resolve after drug discontinuation; others resulted in invasive diagnostic procedures, hospitalization, or prolonged use of systemic corticosteroids or immunosuppressants. One death occurred due to serious cutaneous reaction. Therefore, serious diffuse or inflammatory rashes should be evaluated by a specialist before continuing daclizumab and discontinuation may be appropriate.

Daclizumab also increases infection risk (65% daclizumab vs. 57% interferon group in DECIDE; 50% daclizumab vs. 44% placebo groups SELECT) and depression/suicide (10% daclizumab vs. 8% interferon group in DECIDE; 7% daclizumab vs. 2% placebo group in SELECT). Serious infections occurred in 4% of the daclizumab vs. 2% of the interferon group in DECIDE and 3% of the daclizumab vs. 0% of the placebo group in SELECT. Depression-related events occurred in 0.4% of the daclizumab group versus 0.7% of the interferon group in DECIDE and no patients in SELECT. Therefore, patients at high risk for tuberculosis should be tested and treated if necessary before initiating daclizumab. Daclizumab should be avoided in patients with other active severe infections until resolution. Patients should be tested for hepatitis B and C. Live vaccinations should be considered before and not during treatment. Daclizumab should be given with caution to those with previous or current depressive disorders and discontinued in those who develop severe depression or suicidal ideation.

In controlled studies, one woman treated with daclizumab developed breast cancer but none treated with interferon beta-1a developed breast cancer. Across all controlled and open-label clinical studies, 8 of 1485 (0.5%) women and 1 of 751 (0.1%) men treated with daclizumab developed breast cancer.

Because the exclusion criteria in clinical trials were broad and somewhat subjective (e.g., subjects with history of malignancy, severe allergic reaction, recent serious infection, and significant medical condition in investigator's opinion) and the duration of use of MS drugs is long compared with the duration of the studies, the full extent of the risk for adverse drug reactions (ADR) is unclear. The extent to which ADR rates reflect the incidence in men, non-whites, older patients (age >55 years), and patients with greater disability is unknown, because the study populations were predominantly female, white, and younger and excluded patients with greater disability (EDSS >5).

Pharmacology and Pharmacokinetic Properties: [1]

Parameter	
Mechanism of Action	Precise mechanism of action MS is unknown, but is presumed to involve the modulation of IL-2 mediated activation of lymphocytes via binding to the IL-2 receptor CD25 subunit.
Absorption	Bioavailability is 90% following subcutaneous injection
Distribution and Protein Binding	Vd = 6.34 L; no information available on protein binding
Metabolism	Presumed catabolism to peptides and amino acids
Half-Life	21 days
Elimination	Presumed catabolism to peptides without renal elimination

Abbreviations: Vd = volume of distribution

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:

1) Relapse rate
2) Functional status (i.e., disability)
3) Quality of life
4) Early discontinuation due to adverse event

Primary Study Endpoint:

1) Annualized relapse rate over a period of 96 to 144 weeks (defined as: new or recurrent neurologic symptoms that lasted at least 24 hours; the symptoms had to be accompanied by new objective neurologic findings on examination)

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.DECIDE (Study 301) Kappos, et al. 2015[14] FDA Review[15] Randomized, AC, DB, phase 3 study 244 sites in 28 countries May 2010 to April 2012	1. DAC SC 150 mg q 4 weeks plus PBO IM q 1 week 2. INF IM 30 mcg q 1 week plus PBO SC q 4 weeks Duration: at least 96 weeks and no more than 144 weeks (median 109 weeks for DAC and 111 weeks for INF)	Demographics: (DAC, INF) ·Age (yr): 36, 36 ·Female (%): 68, 68 ·White (%): 90, 90 ·Prior therapy (%): DMD: 41, 41 INF: 34, 34 ·Time since 1st symptoms (yr): 7, 7 ·# relapses in ≤1 yr: 1.6, 1.5 ·EDSS (mean): 2.5, 2.5 ·MSIS-29 physical subscale: 22, 22 Key Inclusion Criteria: ·Diagnosed RRMS ·Age 18 to 55 yrs ·MS lesions on MRI ·EDSS 0 to 5 ·≥2 relapses w/in prior 3 yrs, w/ ≥1 w/in yr before randomized *or* ≥1 relapse and ≥1 new lesion w/o relapse w/in prior 2 yrs, w/ ≥1 of events in yr before randomized ·Contraception for of age women Key Exclusion Criteria: ·H/o malignancy, severe allergic reactions, abnormal lab results that may indicate significant disease	ITT: 1. 919 2. 922 Attrition: 1. 21% 2. 25%	Primary Endpoint: Annualized Relapse Rate: 1. 0.22; 95% CI: 0.19 to 0.24) 2. 0.39; 95% CI: 0.35 to 0.44) RRR 45%; 95% CI, 36 to 53%; p<0.0001 Secondary Endpoints (in rank order of analysis): Adjusted mean # new or newly enlarged T_2 lesions over 96 weeks: 1. 4.3 (n=864) (95% CI: 3.9 to 4.8) 2. 9.4 (n=841) (95% CI: 8.5 to 10.5) RRR 54%; 95% CI: 47 to 61; p<0.0001 Disability progression over 144 weeks:† 1. 16% vs. 2. 20% HR 0.84; 95% CI, 0.66 to 1.07; p=NS No relapse at 144 weeks: 1. 67% vs. 2. 51% HR 0.59; 95% CI, 0.5 to 0.69; p=NA ≥7.5 point MSIS-29 increase from baseline to 96 weeks: 1. 19% 2. 23% RRR 24%; 95% CI, 5 to 40%; p=NA	 NA NA NS NA NA	SAE: 1. 15% 2. 10% Any AE: 1. 91% 2. 91% D/c due to AE: 1. 14% 2. 9% Hepatobiliary disorder: 1. 3% 2. 2% Serious hepatobiliary disorder: 1. 1% 2. <1% Infection 1. 65% 2. 57% Serious infection 1. 4% 2. 2% Cutaneous event 1. 37% 2. 19% Serious cutaneous event 1. 2% 2. <1% Hepatic event 1. 16% 2. 14%	 5%/20 NA 5%/20 1%/100 NA 8/13 2%/50 18%/6 ~1%/100 2%/50	**Risk of Bias (low/high/unclear)**: Selection Bias: LOW. Randomization by centralized interactive voice-response system, stratified by study site and before INF use, using permutated-block randomization ·Characteristic well-balanced between study groups Performance Bias: LOW ·Double dummy design ·Patients told to take prophylactic treatment for influenza-like symptoms for the first 4 weeks to reduce potential unblinding due to INF side effects ·All patient and study personnel blinded to treatment assignments Detection Bias: LOW. Patients told to take prophylactic treatment for influenza-like symptoms for the first 4 weeks to reduce potential unblinding due to INF side effects ·All patient and study personnel blinded to treatment assignments Attrition Bias: HIGH. Missing patient data for hyperintense (14 in INF group and 19 in DAC group) and Gd lesion (13 in the INF group and 19 in DAC group) ·High attrition rate (21% DAC and 25% INF). Mostly driven by withdrawal of consent, AEs, and perceived lack of efficacy ·For relapse rate, censoring was at the earliest of start of alternative MS medication, 180 days after the last dose for patients who d/c treatment, or end of treatment for patients who completed treatment Reporting Bias: UNCLEAR. Supported by Biogen and AbbVie Biotherapeutics, including involvement in data analysis and manuscript preparation · Detailed study protocol published **Applicability**: Patient: Broad and somewhat subjective exclusion criteria, so efficacy and ADR rates may not reflect that in clinical practice

		·Relapse w/in 50 days before randomization or unstable relapse ·Abnormal blood counts, SCr, LFTs ·Recent serious infection ·Use of certain immunomodulating therapy regimens				Severe hepatic event 1. 1% 2. <1%	NA	·About 13% of subjects were in the US and Canada ·Subjects had EDSS ≤5, efficacy in patients with greater disability unknown, which could be a population likely to receive this drug ·Subjects were predominantly female, Caucasian, and younger, so efficacy rates may be different for male, non-Caucasian, and older patients. Also, race was determined by the investigator, potentially increasing error in racial assignment. Intervention: DAC or matching PLA administered in clinic during study, whereas prescription is for self-administration, which may affect effectiveness ·Patients already on an interferon preparation were included and not required to washout before randomization. Also, corticosteroids and glatiramer acetate treatment allowed up to within 30 days before randomization. Therefore, any continuing benefit from these therapies is potential confounder ·Study does not address best time to stop or start drug when to start or stop drug Comparator: Active comparator Outcomes: Relapse rate is a surrogate outcome for disability progression. However, it is used because the EDSS has poor sensitivity ·Study of short duration given the high variability of disease progression in terms of disability and length of time to disease progression and given the AE profile Setting: The monitoring frequency is high and highly trained practitioners are required both for MS and for those who experience ADRs

2.SELECT (Study 201) Gold, et al.[13] FDA Review[15] Randomized, DB, PC, phase 2, dose-ranging study 76 sites in Czech Republic, Germany, Hungry, India, Poland, Ukraine, Turkey, and UK Feb 2008 to May 2010	1. DAC SC 150 mg q 4 weeks 2. DAC SC 300 mg q 4 weeks 3. PBO SC q 4 weeks Duration: 52 weeks (13 doses)	Demographics: ·DAC 150, DAC 300, PLA, respectively ·Age (yr): 35, 35, 37 ·Female (%): 67, 64, 63 ·White (%): 97, 96, 97 ·No previous DMD, except steroid (%): 75, 78, 76 ·Time since diagnosis (yrs): 3, 3, 2 ·Relapses in past yr: 1.4, 1.3, 1.3 EDSS: 2.8, 2.7, 2.7 ·# Gd lesions: 2.1, 1.4, 2 ·≥1 Gd lesions (%): 51, 36, 44 ·# T_2 hyperintense lesions: 45, 36, 40 Key Inclusion Criteria: ·Age 18 to 55 years ·RRMS ·EDSS ≤5 ·≥1 MS relapse in the year before randomized *or* ≥1 new Gd lesions on MRI w/in 6 weeks before randomized Key Exclusion Criteria: ·Severe allergic or reactions or drug hypersensitivity ·History malignancy ·Significant medical condition in investigator's opinion	ITT: 1. 201 2. 203 3. 196 Attrition: 1. 18 2. 19 3. 17	Primary Endpoint: Annualized Relapse Rate: 1. 0.21; 95% CI, 0.16 to 0.29 RR vs PBO 0.46; 95% CI, 0.32 to 0.67; p<0.001 2. 0.23; 95% CI, 0.17 to 0.31 RRR vs PBO 50%; 95% CI, 35 to 72%; p=0.0002 3. 0.46; 95% CI, 0.37 to 0.57 Secondary Endpoints (in rank order): Mean total # Gd lesions at weeks 8, 12, 16, 20, and 24 in a subset of 307 patients: 1. 1.5; 95% CI, 1.1 to 2.0 (n=101) RRR 69% vs PBO; 95% CI, 52.4 to 80.4%; p<0.0001 2. 1.0; 95% CI, 0.7 to 1.5 (n=102) RRR 78% vs PBO; 95% CI, 66 to 86.4%; p<0.0001 3. 4.8; 95% CI, 3.6 to 6.4 (n=104) Mean # new or newly enlarged T_2 hyperintense lesions at 52 weeks: 1. 2.4; 95% CI, 2.0 to 3.0 (n=199) RRR 70% vs PBO; 95% CI, 59.4 to 77.9%; p<0.0001 2. 1.7; 95% CI, 1.4 to 2.2 (n=200) RRR 79% vs PBO; 95% CI, 71.3 to 84.2%; p<0.0001)	NA NA NA NA NA NA NA	SAE 1. 7% 2. 9% 3. 6% Any AE 1. 73% 2. 76% 3. 79% Death 1. <1%% 2. 0% 3. 0% Serious infection 1. 3% 2. 1% 3. 0% Infection 1. 50% 2. 54% 3. 44% Serious cutaneous events 1. <1% 2. <1% 3. 0% Cutaneous events 1. 18% 2. 22% 3. 13% Other immune-mediated SAE 1. 0% 2. 2% 3. 0% ALT or AST >3X ULN 1. 3% 2. 3% 3. <1%	1%/100 3%/34 NA NA NA NA 3%/34 1%/100 6%/17 10%/10 NA NA 5%/20 9%/11 NA 2%/50 3%/34 3%/34	**Risk of Bias (low/high/unclear)**: Selection Bias: LOW. Uneven across treatment groups for % of subjects with ≥1 Gd lesions and hyperintense lesions. However, patients on the selected dosage of DAC is the group with more advanced disease ·Randomization by centralized interactive voice response system Performance Bias: LOW. All personnel and patients blinded to treatment assignment, except pharmacist Detection Bias: LOW. All personnel and patients blinded to treatment assignment, except pharmacist Attrition Bias: HIGH. ITT population includes all randomized subjects who received ≥1 dose study drug, except for 21 subjects from a site closed due to mis-dosing (5 in DAC 300, 8 in DAC 150, and 8 in PLA groups) ·High attrition rate. Mostly driven by withdrawal of consent and AEs for the DAC arms and withdrawal of consent for PLA arm Reporting Bias: UNCLEAR ·Sponsor (Biogen and AbbVie) designed study, held and analyzed data, and participated in data interpretation and manuscript preparation · Detailed study protocol not published **Applicability**: Patient: No subjects in US ·Subjects had EDSS ≤5, efficacy in patients with greater disability unknown, which could be a population likely to receive this drug ·Subjects were predominantly female, Caucasian, and younger. Therefore, efficacy rates may be different for male, non-Caucasian, and older patients. · Broad and subjective exclusion criteria, so efficacy and ADR rates may not reflect what occurs in clinical practice Intervention: Subjects permitted to add INF as a treatment for relapse during the study after Month 6 (n=1 for each DAC group and n=5 in PLA group) Comparator: Nonactive comparator

		·Use of certain immunomodulating therapy regimens		3. 8.1; 95% CI: 6.7 to 9.9 (n=195) <u>% with relapse</u>: 1. 19% HR 0.45 (95% CI, 0.3 to 0.67; p<0.0001) 2. 20% HR 0.49 (95% CI: 0.33 to 0.72; p=0.00032) 3. 36% QOL (change in MSIS-29 physical impact score from baseline to Week 52): 1. -1 (SD 11.8) p = 0.000082 2. 1.4 (SD 13.5) p=0.13 3. 3 (SD 13.5)	17%/6 16%/7 NS* NS*	<u>Malignancy</u> 1. <1% 2. <1% 3. <1%	NA NA	<u>Outcomes</u>: Relapse rate is a surrogate outcome for disability progression. However, it is used because the EDSS has poor sensitivity. However, EDSS is often assessed as a secondary endpoint. In this study, it was a tertiary endpoint (data not reported here). ·Study of short duration given the high variability disease progression in terms of disability and length of time to disease progression and given the AE profile <u>Setting</u>: The monitoring frequency is high and highly trained practitioners are required both for MS and for those who experience ADRs.

<u>Abbreviations</u> [alphabetical order]: AC = active controlled; ADR=adverse drug reaction; AE=adverse event; ARR = absolute risk reduction; CI = confidence interval; d/c = discontinuation; DAC = daclizumab; DMD: disease modifying drug; EDSS = Expanded Disability Status Score (range from 0 to 10, with higher scores indicating worse disability); hgb = hemoglobin; IM = intramuscular; INF = interferon beta-1a; Gd: gadolinium-enhancing; IM = intramuscular; ITT = intention to treat (patient randomized and received ≥1 dose study drug); LFT = liver function tests; mITT = modified intention to treat; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSIS-29 = 29-item MS Impact Scale (range from 1 to 100, with higher scores indicating a greater physical or psychological effect of MS from the patient's perspective); N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = not significant; PBO = placebo; PC = placebo controlled; PP = per protocol; q = every; QOL = quality of life; RR = rate ratio; RRR = relative risk reduction; RRMS = relapsing remitting multiple sclerosis; SCr = creatinine clearance; SC = subcutaneous; SAE = serious adverse event; ULN = upper limit of normal; US = United States; WBC = white blood cell count

*NS due to use of sequential closed-testing procedure to control for type I error that could result from multiple comparisons

†Disability progress = ≥1 point increase from baseline score of ≥1 or an increase ≥1.5 from a baseline score of 0 on EDSS at 12 weeks

References:

1. Zinbryta [daclizumab] prescribing information. Biogen: Cambridge, Massachusetts. May 2016.
2. Campbell JD, Ghushchyan V, Brett McQueen R, et al. Burden of multiple sclerosis on direct, indirect costs and quality of life: National US estimates. *Multiple Sclerosis and Related Disorders*. 2014;3(2):227-236.
3. Patwardhan MB, Matchar DB, Samsa GP, McCrory DC, Williams RG, Li TT. Cost of multiple sclerosis by level of disability: a review of literature. *Multiple sclerosis (Houndmills, Basingstoke, England)*. 2005;11(2):232-239.
4. Adelman G, Rane SG, Villa KF. The cost burden of multiple sclerosis in the United States: a systematic review of the literature. *Journal of medical economics*. 2013;16(5):639-647.
5. Goodin DS, Frohman EM, Garmany, G P, Jr, et al. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. *Neurology*. 2002;58(2):169-178.
6. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83(3):278-286.
7. Wingerchuk DM, Carter JL. Multiple sclerosis: current and emerging disease-modifying therapies and treatment strategies. *Mayo Clinic proceedings*. 2014;89(2):225-240.
8. Pittock SJ, McClelland RL, Mayr WT, et al. Clinical implications of benign multiple sclerosis: a 20-year population-based follow-up study. *Annals of neurology*. 2004;56(2):303-306.
9. Wiendl H, Meuth SG. Pharmacological Approaches to Delaying Disability Progression in Patients with Multiple Sclerosis. *Drugs*. 2015;75(9):947-977.
10. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*. 1983;33(11):1444-1452.
11. Mitsikostas DD. Methodology of clinical trials in multiple sclerosis. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*. 2006;27 Suppl 5:S362-4.
12. Canadian Agency for Drugs and Technologies in Health. CADTH therapeutic review. Recommendations for drug therapies for relapsing-remitting multiple sclerosis [Internet]. Ottawa: The Agency, 2013 Oct. (CADTH Therapeutic Review vol.1, no. 2c). [cited 2016 12 04]. Available from: http://www.cadth.ca/media/pdf/TR0004_RRMS_RecsReport_TR_e.pdf.
13. Gold R, Giovannoni G, Selmaj K, et al. Daclizumab high-yield process in relapsing-remitting multiple sclerosis (SELECT): a randomised, double-blind, placebo-controlled trial. *Lancet (London, England)*. 2013;381(9884):2167-2175.
14. Kappos L, Wiendl H, Selmaj K, et al. Daclizumab HYP versus Interferon Beta-1a in Relapsing Multiple Sclerosis. *The New England journal of medicine*. 2015;373(15):1418-1428.
15. Food and Drug Administration Center for Drug Evaluation and Research. Application Number: 761029Orig1s000 Medical Review. http://www.accessdata.fda.gov/scripts/cder/daf/. Accessed September 10, 2016.

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
SUB-Q	SYRINGE	COPAXONE	GLATIRAMER ACETATE	Y
INTRAMUSC	KIT	AVONEX ADMINISTRATION PACK	INTERFERON BETA-1A/ALBUMIN	Y
SUB-Q	SYRINGE	REBIF	INTERFERON BETA-1A/ALBUMIN	Y
SUB-Q	PEN INJCTR	REBIF REBIDOSE	INTERFERON BETA-1A/ALBUMIN	Y
INTRAMUSC	PEN IJ KIT	AVONEX PEN	INTERFERON BETA-1A	Y
INTRAMUSC	SYRINGE	AVONEX	INTERFERON BETA-1A	Y
INTRAMUSC	SYRINGEKIT	AVONEX	INTERFERON BETA-1A	Y
SUB-Q	KIT	BETASERON	INTERFERON BETA-1B	Y
SUB-Q	KIT	EXTAVIA	INTERFERON BETA-1B	Y
INTRAVEN	VIAL	LEMTRADA	ALEMTUZUMAB	N
SUB-Q	SYRINGE	ZINBRYTA	DACLIZUMAB	N
ORAL	TAB ER 12H	AMPYRA	DALFAMPRIDINE	N
ORAL	CAPSULE DR	TECFIDERA	DIMETHYL FUMARATE	N
ORAL	CAPSULE	GILENYA	FINGOLIMOD HCL	N
SUB-Q	SYRINGE	GLATOPA	GLATIRAMER ACETATE	N
INTRAMUSC	PEN INJCTR	AVONEX PEN	INTERFERON BETA-1A	N
SUB-Q	VIAL	EXTAVIA	INTERFERON BETA-1B	N
INTRAVEN	VIAL	MITOXANTRONE HCL	MITOXANTRONE HCL	N
SUB-Q	SYRINGE	PLEGRIDY	PEGINTERFERON BETA-1A	N
SUB-Q	PEN INJCTR	PLEGRIDY PEN	PEGINTERFERON BETA-1A	N
ORAL	TABLET	AUBAGIO	TERIFLUNOMIDE	N

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

ZINBRYTA (daclizumab) injection, for subcutaneous use
Initial U.S. Approval: 2016

WARNING: HEPATIC INJURY INCLUDING AUTOIMMUNE HEPATITIS and OTHER IMMUNE-MEDIATED DISORDERS
See full prescribing information for complete boxed warning.

Hepatic Injury Including Autoimmune Hepatitis
- **ZINBRYTA can cause severe liver injury including life-threatening events, liver failure, and autoimmune hepatitis. Obtain transaminase and bilirubin levels before initiation of ZINBRYTA. Monitor and evaluate transaminase and bilirubin levels monthly and up to 6 months after the last dose (2.3, 2.4, 5.1).**
- **ZINBRYTA is contraindicated in patients with pre-existing hepatic disease or hepatic impairment (4, 5.1).**

Other Immune-Mediated Disorders
- **Immune-mediated disorders including skin reactions, lymphadenopathy, non-infectious colitis, and other immune-mediated disorders can occur with ZINBRYTA (5.2).**

These conditions may require treatment with systemic corticosteroids or immunosuppressive medication (5.1, 5.2).

ZINBRYTA is available only through a restricted distribution program called the ZINBRYTA REMS Program (5.3).

INDICATIONS AND USAGE

ZINBRYTA is an interleukin-2 receptor blocking antibody indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (MS). Because of its safety profile, the use of ZINBRYTA should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS. (1)

DOSAGE AND ADMINISTRATION

- Recommended dosage: 150 milligrams once monthly (2.1)
- For subcutaneous use only (2.1)
- Train patients in the proper technique for self-administration (2.2)
- Conduct laboratory tests at baseline and at periodic intervals to monitor for early signs of potentially serious adverse reactions (2.3, 2.4).

DOSAGE FORMS AND STRENGTHS

Injection: 150 mg/mL solution in a single-dose prefilled syringe (3)

CONTRAINDICATIONS

- Pre-existing hepatic disease or hepatic impairment, including ALT or AST at least 2 times the ULN (4)
- History of autoimmune hepatitis or other autoimmune condition involving the liver (4)
- History of hypersensitivity to daclizumab or any other component of the formulation (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity Reactions: Risk of anaphylaxis and angioedema. Discontinue and do not re-start ZINBRYTA if anaphylaxis or other allergic reactions occur (5.4)
- Infections: Increased risk of infections. If serious infection develops, consider withholding ZINBRYTA until infection resolves (5.5)
- Depression and Suicide: Advise patients to immediately report symptoms of depression and/or suicidal ideation to their health care provider. Consider discontinuation if severe depression and/or suicidal ideation occur (5.6)

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥5% and ≥2% higher incidence than comparator) reported for ZINBRYTA were nasopharyngitis, upper respiratory tract infection, rash, influenza, dermatitis, oropharyngeal pain, bronchitis, eczema and lymphadenopathy compared with AVONEX; and upper respiratory tract infection, depression, rash, pharyngitis, and increased alanine aminotransferase (ALT) compared with placebo (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Biogen at 1-800-456-2255 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Hepatotoxic Drugs: Evaluate potential for increased risk of hepatotoxicity with concomitant use (7.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 05/2016

Table 2: Adverse Reactions in Adults with RMS with an Incidence at Least 2% More for ZINBRYTA 150 mg SQ Every 4 Weeks than AVONEX 30 mcg IM Once Weekly (Study 1)

Adverse Reaction	ZINBRYTA 150 mg SQ Every 4 Weeks N=919 %	AVONEX 30 mcg IM Once Weekly N=922 %
Nasopharyngitis	25	21
Upper respiratory tract infection [1]	17	14
Rash [2]	11	4
Influenza	9	6
Dermatitis [3]	9	2
Oropharyngeal pain	8	4
Bronchitis	7	5
Eczema [4]	5	2
Lymphadenopathy	5	<1
Tonsillitis	4	2
Acne	3	<1

[1] includes upper respiratory tract infection and viral upper respiratory tract infection
[2] includes erythematous rash, exfoliative rash, macular rash, maculopapular rash, papular rash, pruritic rash, rash, and vesicular rash
[3] includes allergic dermatitis, atopic dermatitis, bullous dermatitis, dermatitis, exfoliative dermatitis, and seborrheic dermatitis
[4] includes dyshidrotic eczema, eczema, and nummular eczema

Table 3: Adverse Reactions in Adults with RMS with an Incidence at Least 2% More for ZINBRYTA 150 mg SQ Every 4 Weeks than Placebo (Study 2)

Adverse Reaction	ZINBRYTA 150 mg SQ Every 4 Weeks N=208 %	Placebo N=204 %
Upper Respiratory Tract Infection	9	7
Depression[1]	7	2
Rash[2]	7	3
Pharyngitis	6	4
Increased ALT	5	2
Rhinitis	4	1
Anemia	3	<1
Pyrexia	3	<1
Increased AST	3	<1
Dermatitis[3]	3	<1

[1] includes depressed mood and depression
[2] includes erythematous rash, exfoliative rash, macular rash, maculopapular rash, papular rash, pruritic rash, rash, and vesicular rash
[3] includes allergic dermatitis, atopic dermatitis, bullous dermatitis, dermatitis, exfoliative dermatitis, and seborrheic dermatitis

Daclizumab (Zinbryta™)

Goal(s):

- Restrict use of daclizumab to patients with relapsing multiple sclerosis (RMS) who have failed multiple drugs for the treatment of RMS.
- Ensure appropriate baseline monitoring to minimize patient harm.

Length of Authorization:

6 months

Requires PA:

- Zinbryta™ (daclizumab)

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 patient an adult (age ≥18 years) diagnosed with relapsing multiple sclerosis (RMS)?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Has the patient failed trials for at least 2 drugs indicated for the treatment of RMS?	**Yes:** Document drug and dates trialed: 1._____(dates) 2._____(dates) (3.)_____(dates) (4.)_____(dates) Go to #4	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
4. Does the patient have a higher degree of ambulatory ability (e.g., Expanded Disability Status Scale score ≤5)	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Does the patient have hepatic disease or hepatic impairment, including ALT or AST ≥2-times the upper limit of normal, or have a history of auto-immune hepatitis?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #6
6. Is the prescriber a neurologist who regularly treats RMS?	**Yes:** Approve 150 mg once monthly for 6 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: *1/17*
Implementation: *TBD*

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
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New Drug Evaluation: **pimavanserin** tablet, oral

Date of Review: January 2017
Generic Name: pimavanserin
PDL Class: Antipsychotics, Second Generation

End Date of Literature Search: September 28, 2016
Brand Name (Manufacturer): Nuplazid™ (Acadia Pharmaceuticals)
AMCP Dossier Received: yes

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

Research Questions:
- What is the evidence for efficacy of pimavanserin for the treatment of hallucinations and delusions associated with Parkinson's disease (PD) psychosis and how does it compare to current therapy?
- Is pimavanserin safe for the treatment of PD psychosis?
- Are there subpopulations of adults (i.e. age, gender, ethnicity, disease duration or severity) for whom pimavanserin is more effective or associated with more harms?

Conclusions:
- There is low quality evidence based on one 6-week randomized controlled trial (RCT) that pimavanserin is associated with statistical improvement in the Scale for the Assessment of Positive Symptoms in Parkinson's disease (SAPS-PD), a new clinical instrument designed and modified during phase 2 and 3 clinical trials to assess reduction in hallucinations and delusions in patients with PD. In patients with weekly hallucinations or delusions lasting at least a month, 14% of patients in the pimavanserin group (vs. 1% in the placebo group) had a complete response (defined as a SAPS-PD score of 0) at the end of treatment (NNT=8).[1]
- There is insufficient evidence comparing pimavanserin to other therapies for the treatment of PD psychosis or to evaluate efficacy in subpopulations.
- There is insufficient evidence for the treatment of psychosis associated with other conditions (e.g., schizophrenia) or for PD symptoms other than hallucinations and delusions (e.g., tremor, rigidity, etc.).
- Pimavanserin FDA labeling has a boxed warning for increased mortality in elderly patients with dementia-related psychosis. In clinical trials in patients with PD psychosis, pimavanserin use was associated with a numerically greater number of serious adverse events and death.[1] There is insufficient evidence to evaluate long term safety of pimavanserin for the treatment of PD psychosis and long-term data are needed to determine the significance of harms observed in short-term phase 3 trials.

Recommendations:
- A safety edit to restrict use to populations that may benefit from this drug without undue harms is proposed in **Appendix 3**.

Background:
Parkinson's disease (PD) is a progressive disease characterized by loss of dopaminergic neurons in the substantia nigra, the motor center of the brain.[2,3] Exact etiology of PD is unclear, but it has been associated with defects in the parkin gene, tau gene or alpha-synuclein proteins which can cause nerve damage characteristic of PD and lead to common neuromuscular signs of PD.[3] Diagnosis is typically based on clinical signs and symptoms including symptoms of bradykinesia, muscular rigidity, resting tremor and postural instability.[2] Loss of dopaminergic neurons in other parts of the brain can also lead to non-motor symptoms including decreased autonomic function, fatigue, sleep disturbances, mood disorders, and erectile dysfunction.[2] Long-term complications of PD include dementia, psychosis, hallucinations and delusions. Up to 40-50% of patients with PD experience thinking, behavioral problems or psychosis.[1] Generally, presence of hallucinations indicates a worsening prognosis over time.[4,5] In a small study (n=48), 81% of patients with minor "benign" hallucinations had progressive symptoms characterized by delusions or loss of insight within 3 years.[6] Presence of psychosis symptoms has also been positively associated with nursing home admission.[4,7]

Currently there are no FDA-approved therapies for treatment of PD psychosis. Guidelines from the American Academy of Neurology for psychosis in PD recommend off-label use of clozapine or quetiapine.[8] The guidelines note that clozapine is probably an effective treatment as it demonstrated superior improvement in psychosis symptoms compared to placebo in at least 1 RCT.[8] However, because clozapine is associated with serious adverse effects and requires frequent monitoring, it may not be an optimal treatment for many patients. Guidelines also recommend quetiapine as a treatment option.[8] However, while quetiapine is generally well tolerated, it has not demonstrated consistent efficacy compared to placebo for reduction of symptoms associated with PD psychosis.[9]

In 2016, the FDA approved pimavanserin as the first treatment for hallucinations and delusions associated with Parkinson's disease. Pimavanserin acts as a selective inverse agonist and antagonist at serotonin 5-HT_{2A} and 5-HT_{2C} receptors.[10] In patients with PD, these receptors are located in high concentrations in the visual and auditory areas of the brain and are thought to be linked with psychosis symptoms.[11] Theoretically, selective blockade of these receptors will decrease psychosis symptoms without causing any adverse motor effects associated with dopamine blockade. This is especially important in PD because many antipsychotics, including clozapine and quetiapine, have dopamine antagonist effects and have the potential to worsen motor symptoms of Parkinson's disease. Ongoing trials are also examining pimavanserin for psychosis related to Alzheimer's disease and as adjuvant therapy in addition to other antipsychotics in schizophrenia.[12]

Pimavanserin achieved accelerated approval as a breakthrough therapy for PD psychosis primarily on the results from one phase 3 trial of 199 patients with PD and persistent hallucinations or delusions severe enough to warrant antipsychotic therapy.[11] Data from additional phase 2 studies, unpublished phase 3 trials, and open-label extension studies were used to assess safety. During these trials approximately 278 patients were exposed pimavanserin for more than 12 months and 141 for more than 24 months.[1] In the single published phase 3 trial, patients were randomized to pimavanserin 34 mg daily or placebo and followed for 6 weeks.[11] In this trial, symptom improvement was assessed using a newly developed tool called the Scale for the Assessment of Positive Symptoms in Parkinson's disease (SAPS-PD).[11] There is currently no universally used scale to assess symptoms in PD,[8] and the tools used to assess hallucinations and delusions in PD psychosis have evolved over the course of these clinical trials. Initial phase 3 trials utilized the Scale for the Assessment of Positive Symptoms sections for hallucinations and delusions (SAPS-HD) to assess symptom improvement. Due to lack of improvement with use of this scale in these trials, the assessment tool was further modified to the Scale for the Assessment of Positive Symptoms in Parkinson's disease (SAPS-PD).[11] The SAPS-PD is a 9-item questionnaire which specifically assesses the frequency or severity of the most common types of hallucinations or delusions; namely, auditory hallucinations, voices conversing, somatic or tactile hallucinations, visual hallucinations, persecutory delusions, delusions of jealousy, and delusions of reference.[13] The SAPS-PD also includes a

global assessment for hallucinations and delusions.[13] Each item is rated on a 0 to 5 scale with a total assessment range of 0 to 45.[13] Prior to this trial, the SAPS-PD score had not been prospectively evaluated in a trial. In order to establish consistent efficacy compared to other assessment scales, the Clinical Global Impression-Improvement scales for improvement (CGI-I) and severity (CGI-S) were also evaluated as exploratory outcomes.[11] Upon retrospective comparison of the SAPS-PD and CGI-I scales in a population of phase 3 patients with PD, a 1 point change in the CGI-I scale, was associated with a 2.33 reduction in SAPS-PD score.[13] CGI-I scores evaluate symptom improvement on a 1-7 scale with a change of 1 corresponding to a minimally improved change in symptoms.[14] Complete improvement in symptoms (defined as a SAPS-PD score of 0 at the end of treatment) was also assessed in a post-hoc analysis by FDA. Activities of daily living and adverse motor symptoms were assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) sections 2 and 3. Using these scales, individual items related to motor function and daily activities are rated on a 0-4 scale with higher scores indicating mores severe disease. Exact assessment of disease severity has not been established, but some studies suggest that mild disease corresponds to scores of less than 12 or 16 for daily activities or less than 32 for motor function.[15,16] Similarly, severe disease corresponds to scores greater than 29 or 32 for daily activities and 58 for motor function.[15,16]

Pimavanserin is the first drug FDA approved for the treatment of hallucinations and delusions associated with PD. This document examines the efficacy and safety supporting use of pimavanserin in PD psychosis and makes recommendations for PDL status and PA criteria.

See **Appendix 2** for **Highlights of Prescribing Information** from the manufacturer, including Black Boxed Warning and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Pimavanserin was approved primarily on the basis of a single phase 3 clinical trial.[11] The primary outcome in this trial was change in SAPS-PD score at 6 weeks. This study also examined efficacy using the CGI scales for improvement and severity of symptoms and the UPDRS scales for daily activity level and motor function. Because the SAPS-PD scoring tool has not been previously validated and this trial only demonstrated a modest improvement in the SAPS-PD score, the FDA also looked at post-hoc analyses of patients who achieved complete resolution of their symptoms.[1]

Patients involved in this trial were a mean 72 years of age and had symptoms of PD psychosis lasting at least 1 month.[11] Only patients with frequent symptoms (occurring at least weekly) and symptoms severe enough to necessitate medical treatment were included in the trial.[11] Baseline SAPS-PD score was 14.7 (standard deviation [SD] 5.55) for placebo group and 15.9 (SD 6.12) for pimavanserin.[11] Patients were excluded if they had psychosis due to other disorders, dementia, baseline cognitive dysfunction, uncontrolled serious mental illness or were taking concurrent medications including antipsychotics, anticholinergics or QT-prolonging medications.[11] Approximately 18% had previously been on an antipsychotic within 21 days of trial enrollment.[11] Because dopaminergic treatments for PD may also exacerbate psychosis symptoms, patients were required to be on a stable medication regimen for their disease.[11] The study was also designed with a 2 week run-in period before randomization in order to elicit a placebo response. Prior trials had demonstrated a significant placebo response, limiting investigator's ability to detect significant differences between groups.[17] During the 2 week run-in period, patients received non-pharmacological psychosocial therapy consisting of daily interactions between the patient and their caregiver.[11] The therapy was intended to provide baseline standard of care prior to the treatment phase and to help the patient and caregiver manage psychosis symptoms.[17] Patients who responded to psychosocial therapy (assessed based on SAPS-PD score) were also excluded from the trial.[11] The exact number of patients excluded due to response to non-pharmacological therapy was not reported, but overall 36.6% (n=115) of patients screened were excluded from the study, and 16.9% (n=53) failed to meet baseline inclusion criteria for symptom severity (SAPS-PD score ≥3 out of 5 in at least one global symptom and one specific symptom, or a neuropsychiatric inventory score >4 for hallucination and/or delusion items).[11] Continuation of the non-pharmacological psychosocial therapy was not required during the 6-week treatment period, but the caregiver was involved in

all follow-up visits.[17] Inclusion of this run-in period may limit applicability to real-world populations and highlights that non-pharmacological psychosocial therapy many improve symptoms in some patients.

Overall, the phase 3 study used for FDA approval had moderate risk of bias. The study was a randomized, double blinded, placebo-controlled trial. Methods to randomize patients appeared adequate, but differences in baseline characteristics were still present, notably in gender (42% female in placebo vs. 33% in the pimavanserin group), time since first PD psychosis symptoms (5.5 months longer in placebo group), and stereotactic surgery (11% in pimavanserin vs. 3% in placebo).[11] The clinical implications of these differences are unclear. With greater time since diagnosis of PD psychosis, patients randomized to placebo may have had more progressive disease resulting in a more conservative estimate of the treatment effect. All patients and assessors were blinded to treatment assignment. However, the subjective assessment of symptom improvement increases risk of bias. Because adverse events were more common in the pimavanserin group, risk of unblinding and knowledge of treatment assignment is higher. Attrition was relatively low compared to other studies conducted in populations with PD psychosis with 15.2% of patients in the pimavanserin group versus 7.4% in the placebo group who withdrew from the study.[11] Multiple sensitivity analyses conducted using last-observation-carried-forward, worst-observation-carried-forward and mixed model repeated measures analysis all resulted in similar effect size, indicating low attrition bias. Protocol violations were noted in 6 patients (5 in the pimavanserin group) who took quetiapine or clozapine during the trial which may bias results in favor of the treatment group.[17] Risk of reporting bias was high. This study was funded by Acadia Pharmaceuticals who was involved in trial design, governance, statistical analysis and publication. In addition, 2 prior unpublished phase 3 studies (NCT00477672, NCT00658567) using alternate assessment methods for symptom improvement (primarily SAPS-HD) did not demonstrate statistical significance compared to placebo.[12]

Pimavanserin demonstrated a mean 3.06 point reduction in SAPS-PD score compared to placebo at 6 weeks (95% CI -4.91 to -1.20; p-value 0.0014).[11] Total scores on the SAPS-PD scale can range from 0 to 45. A statistical difference between groups was apparent at week 4 and continued until treatment discontinuation.[1] Similar trends in symptom improvement were observed in CGI-I (RD -0.67, 95% CI -1.06 to -0.27; p=0.0011) and CGI-S (RD -0.58, 95% CI -0.92 to -0.25; p=0.0007), though these are not clinically meaningful reductions.[11] In a post-hoc analysis conducted by the FDA of patients who completed 6 weeks of treatment (n=173), 14% of patients in the pimavanserin group (vs 1% in placebo group) had a complete response (defined as a SAPS-PD score of 0) at the end of treatment.[1] However, this analysis did not account for patients who discontinued the trial before completion of 6 weeks (15.2% in pimavanserin vs. 7.4% in placebo groups). Subgroup analyses based on age, gender, and race were similar to results in the overall population.[1]

However, despite the fact that this trial demonstrates statistically significant changes in the SAPS-PD score, questions remain about the efficacy of pimavanserin. Further information is necessary to establish a minimal clinically important difference with SAPS-PD and establish definite correlations with symptom improvement. Data from previous clinical trials suggest that a change of 2.33 points correlates with a clinically significant difference of 1 point in the CGI-I scoring tool.[13] However, review by the FDA suggests that a 5 to 7 point change may be a more accurate assessment of clinical improvement.[17] In this trial, SAPS-PD demonstrated a moderate correlation with CGI-I (Spearman's Rank correlation coefficient [R] 0.6, 95% CI 0.5 to 0.7) and CGI-S (R 0.5, 95% CI 0.4 to 0.6) but no correlation with sleep or psychosis (R<0.2).[11] A lack of correlation with psychosis indicates that SAPS-PD may not be an adequate surrogate marker for overall psychosis symptoms. Because it focuses on specific types of hallucinations and delusions, the SAPS-PD may give more weight to auditory hallucinations and does not evaluate other psychotic symptoms.[17]

Pimavanserin represents a drug with a unique mechanism of action which demonstrates benefit in patients with PD psychosis. Prior to its approval, patients with PD psychosis had few options for treatment. Current standard of care utilize off-label clozapine or quetiapine which either have stringent monitoring parameters or limited efficacy. Pimavanserin use in patients with moderate symptoms of PD psychosis has shown statistical improvement, but its efficacy in patients with

severe psychosis and with treatment durations longer than 6 weeks is still unknown. Further studies designed and powered to examine long-term symptom improvement, clinically relevant outcomes of disease progression or admission to nursing homes, and comparisons to other off-label treatments for PD psychosis would help define pimavanserin's place in therapy.

Clinical Safety:

Safety analyses included patients from multiple controlled trials. Early discontinuation due to adverse events was also more common in patients taking pimavanserin (n=16/202, 8%) compared to placebo (n=10/231, 4%).[10] Rates of most common adverse reactions occurring during clinical trials are listed in Table 1. Serious adverse events occurred more frequently in the pimavanserin group (n=16/202, 8%) compared to placebo (n=8/231, 3.5%).[1] However, serious adverse events were varied with no unifying pathological mechanism and were unlikely to be related to the study drug.[1] In an unpublished open-label extension study of patients previously enrolled in an RCT with pimavanserin (n=459), most common adverse events were falls (26.4%), UTI (16.6%), and hallucinations (13.5%).[18] Median length of follow-up for the extension study was 439 days.[18]

Table 1. Frequency of common adverse effects associated with pimavanserin[10]

	Pimavanserin (n=202)	Placebo (n=231)
Peripheral edema	7%	2%
Nausea	7%	4%
Confusional state	6%	3%
Hallucination (visual, auditory, tactile and somatic)	5%	3%
Constipation	4%	3%
Gait disturbances	2%	<1%

Other adverse events of interest included musculoskeletal effects, QTc-interval prolongation, and mortality in elderly patients with dementia-related psychosis. Because many antipsychotics also have undesired musculoskeletal effects, phase 3 trials specifically examined occurrence of musculoskeletal adverse effects. No differences were observed between placebo and treatment groups (evaluated by UPDRS score).[1] However, development of motor symptoms with long-term treatment greater than 6 weeks remains uncertain. Because motor symptoms typically progress in PD, establishing a causal relationship between long-term motor symptoms and pimavanserin would be challenging. QTc interval was also prolonged in patients taking pimavanserin (mean 5-8 milliseconds) compared to placebo.[1,11] Patients with prolonged QTc interval or those taking concomitant medications known to prolong the QT interval were excluded from the study.[11] Death was more frequent in the pimavanserin group compared to placebo (4 patients vs. 1 patient, respectively), though the number of deaths were too small to be statistically significant.[1] Overall, numbers of patients experiencing these events were small, and cause of death did not have any clear pathology.[1] In all cases, investigators thought cause of death was unlikely or not related to treatment.[1] However, because of the disproportionate increase in serious adverse events and death without an underlying pathological cause, a boxed warning for increased risk of death in elderly patients with dementia related psychosis was included in the labeling. In addition, in animal trials, respiratory distress associated with an increase in phospholipids was observed in animal trials at doses 5-10 times the recommended human dose.[1] No evidence of respiratory problems was observed in clinical trials, but this warning was included in the FDA labeling.[1] No post-marketing risk evaluation is recommended for this drug, but further monitoring of adverse events should be conducted to evaluate long-term safety outcomes in the elderly population. Recommendations from the FDA for Phase 4 post-marketing trials include a randomized withdrawal trial, further evaluation of lung tissue from animals, and drug-drug interaction studies to evaluate effects of CYP3A4 inducers.[1]

Pharmacology and Pharmacokinetic Properties:[10]

Parameter	
Mechanism of Action	Selective inverse agonist and antagonist at serotonin 5-HT_{2A} and 5-HT_{2C} receptors
Absorption	T_{max}: median 6 (range 4-24) hours No significant effect of food on absorption
Distribution and Protein Binding	Mean volume of distribution was 2173 L (SD: 307 L) ~95% dose-dependent protein binding
Metabolism	Metabolism via CYP3A enzymes and to a lesser extent via CYP2J2 and CYP2D6; active metabolite
Half-Life	57 hours, active metabolite of 200 hours
Elimination	Less than 1% eliminate unchanged in the urine, 1.53% eliminated in feces

Abbreviations: SD = standard deviation; T_{max}= time to maximum concentration

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:

1) Improvement or resolution of psychosis symptoms
2) Improvement in quality of life or activities of daily living
3) Mortality
4) Nursing home admission

Primary Study Endpoint:

1) Improvement in symptoms measured by change in SAPS-PD Score

Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
Cummings et al, 2014.[11] Nuplazid FDA Medical Review[17] DB, MC, PC, RCT 2 week run-in period with placebo and psychosocial therapy designed to exclude patients who respond to non-medical therapy	1. Pimavanserin 34 mg daily 2. Placebo Duration: 6 weeks (plus a 2 week run-in period)	Demographics • Mean age: 72 years • BMI: 26.3 kg/m2 • MMSE: 26.3 • Mean UPDRS-II (ADL): 19 • Mean UPDRS-III (motor): 33 • Prior antipsychotic use: 18% • Time since first PDP symptoms: 1. 30.9 months 2. 36.4 months • Female: 1. 33% 2. 42% • Stereotactic surgery 1. 11% 2. 3% Key Inclusion Criteria • Age >40 years • Idiopathic PD >1 year • Diagnosis of PDP (symptoms developing after PD diagnosis) • Severe hallucinations or delusions occurring weekly for duration >1 month requiring medical treatment Key Exclusion Criteria • Psychosis due to other causes or occurring within 6 months of stereotactic surgery • Concurrent dementia, delirium, or uncontrolled mental illness • Non-stable anti-parkinsonian medication regimens • Stroke, MI within 6 months, CHF, prolonged QT or other significant lab abnormalities • Concurrent antipsychotics, anticholinergics, or QT prolonging medications	ITT 1. 105 2. 95 PP 1. 95 2. 90 Attrition 1. 16 2. 7	Primary Endpoint Mean change in SAPS-PD Score (SE) 1. -5.79 (0.66) 2. -2.73 (0.67) RD: -3.06 (95% CI -4.91 to -1.20; p=0.0014) Secondary Endpoints Change in CGI-I Score 1. 2.78 (0.14) 2. 3.45 (0.14) RD: -0.67 (95% CI -1.06 to -0.27; p=0.0011) Change in CGI-S Score 1. -1.02 (0.12) 2. -0.44 (0.12) RD: -0.58 (95% CI -0.92 to -0.25; p=0.0007)	NA NA NA	SAE 1. 11 (11%) 2. 4 (4%) Mortality 1. 2 (2%) 2. 1 (1%) DC due to ADE 1. 10 (9.5%) 2. 2 (2%) p-values NR for safety outcomes	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: LOW. Randomized via preprogramed kit randomization schedule in a block size of 4. Allocation concealment NR. P values NR for baseline characteristics; unable to determine statistical significances. Differences >5% between groups revealed more females in placebo (33 vs 42%) and more stereotactic surgery in pimavanserin group (11 vs 3%). Mean time since first PDP symptoms was greater in placebo (5.5 months). Differences may lead to a more conservative estimate of treatment effect. Performance Bias: LOW. Patients blinded with use of matching placebo. Outcome assessors (central assessor, site assessors, and caregivers) were blinded. Detection Bias: LOW. Subjective outcomes increases risk of bias, but all assessors were blinded. SAPS-PD assessed by a centralized, independent, blinded interviewer via videoconference. Attrition Bias: LOW. Attrition higher in treatment group (15.2% vs 7.4%). Analysis done with MMRM, LOCF, & WOCF in both PP & ITT populations with similar results. Crossovers & adherence were NR. 6 patients (5 taking pimavanserin) took quetiapine or clozapine during the trial which may bias results in favor of pimavanserin.[17] Reporting Bias: HIGH. Funded by Acadia Pharmaceuticals who were involved in trial design, governance, statistical analysis and publication. 2 unpublished phase 3 trials were identified. **Applicability**: Patient: Narrow inclusion criteria limit applicability in patients with comorbid conditions and in patients with infrequent symptoms (16.9% of patients did not meet baseline symptom criteria). Intervention: Run-in period excluded patients with response to non-pharmacological therapy. Efficacy/safety beyond 6 weeks is unclear. Comparator: Placebo is appropriate to establish efficacy. Outcomes: Multiple scales used to assess symptom improvement. SAPS-PD is not validated and the minimum important difference is unclear. SAPS-PD focuses on the most common symptoms and may not correlate to a general improvement in psychosis symptoms. Setting: 52 hospitals and research centers in the US and Canada.

Abbreviations [alphabetical order]: ADE = adverse drug event; ADL = activities of daily living; ARR = absolute risk reduction; BMI = body mass index; CI = confidence interval; CGI-I = clinical global impression improvement; CGI-S = clinical global impression severity; DB = double-blind; DC = discontinuation; FDA = food and drug administration; ITT = intention to treat; LOCF = last observation carried forward; mITT = modified intention to treat; MMRM = mixed model repeated measures analysis; MMSE = mini-mental status examination; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; PC = placebo-controlled; PDP = Parkinson's disease psychosis; PP = per protocol, RCT = randomized control trial; SAE = serious adverse events; SAPS-PD = Parkinson's disease-adapted scale for assessment of positive symptoms; SE = standard error; UPDRS = unified Parkinson's disease rating scale; WOCF = worst observation carried forward.

References:

1. Nuplazid Summary Review. US Food and Drug Administration Center for Drug Evaluation and Research. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/207318Orig1s000SumR.pdf. Accessed July 20, 2016.
2. National Institute for Health and Clinical Excellence. Parkinson's Disease: National Clinical Guideline for Diagnosis and Management in Primary and Secondary Care. London: Royal College of Physicians (UK); 2006.
3. DynaMed [internet database]. Ipswich, MA: EBSCO Publishing, Inc. Updated April 29, 2016. Accessed August 15, 2016.
4. Fenelon G, Alves G. Epidemiology of psychosis in Parkinson's disease. *J Neurol Sci.* 2010;289(1-2):12-17.
5. Rabey JM. Hallucinations and psychosis in Parkinson's disease. *Parkinsonism Relat Disord.* 2009;15 Suppl 4:S105-110.
6. Goetz CG, Fan W, Leurgans S, Bernard B, Stebbins GT. The malignant course of "benign hallucinations" in Parkinson disease. *Arch Neurol.* 2006;63(5):713-716.
7. Aarsland D, Larsen JP, Tandberg E, Laake K. Predictors of nursing home placement in Parkinson's disease: a population-based, prospective study. *J Am Geriatr Soc.* 2000;48(8):938-942.
8. Miyasaki JM, Shannon K, Voon V, et al. Practice Parameter: Evaluation and treatment of depression, psychosis, and dementia in Parkinson disease (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* 2006;66(7):996-1002.
9. Friedman JH. Parkinson's disease psychosis 2010: A review article. *Parkinsonism Relat Disord.* 2010;16(9):553-560.
10. Nuplazid - pimavanserin tartrate tablet, coated [package insert]. San Diego, CA: Acadia Pharmaceuticals, Inc; 2016.
11. Cummings J, Isaacson S, Mills R, et al. Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. *Lancet.* 2014;383(9916):533-540.
12. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/results?term=pimavanserin&Search=Search. Accessed October 17, 2016.
13. Voss T, Bahr D, Cummings J, Mills R, Ravina B, Williams H. Performance of a shortened Scale for Assessment of Positive Symptoms for Parkinson's disease psychosis. *Parkinsonism Relat Disord.* 2013;19(3):295-299.
14. Martinez-Martin P. Instruments for holistic assessment of Parkinson's disease. *Journal of neural transmission (Vienna, Austria : 1996).* 2013;120(4):559-564.
15. Martinez-Martin P, Rodriguez-Blazquez C, Mario A, et al. Parkinson's disease severity levels and MDS-Unified Parkinson's Disease Rating Scale. *Parkinsonism Relat Disord.* 2015;21(1):50-54.
16. Rodriguez-Blazquez C, Rojo-Abuin JM, Alvarez-Sanchez M, et al. The MDS-UPDRS Part II (motor experiences of daily living) resulted useful for assessment of disability in Parkinson's disease. *Parkinsonism Relat Disord.* 2013;19(10):889-893.
17. Nuplazid Medical Review. US Food and Drug Administration Center for Drug Evaluation and Research. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/207318Orig1s000MedR.pdf. Accessed October 3, 2016.
18. Nuplazid (pimavanserin) tablets [product dossier]. San Diego, CA: Acadia Pharmaceuticals Inc.; 2016.

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL	Carveout
ORAL	TABLET	CLOZAPINE	CLOZAPINE	Y	Y
ORAL	TABLET	CLOZARIL	CLOZAPINE	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
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	ARIPIPRAZOLE	ARIPIPRAZOLE	V	Y
ORAL	TABLET	ABILIFY	ARIPIPRAZOLE	V	Y
ORAL	SOLUTION	ARIPIPRAZOLE	ARIPIPRAZOLE	V	Y
ORAL	TAB RAPDIS	ARIPIPRAZOLE ODT	ARIPIPRAZOLE	V	Y
SUBLINGUAL	TAB SUBL	SAPHRIS	ASENAPINE MALEATE	V	Y
ORAL	TABLET	REXULTI	BREXPIPRAZOLE	V	Y
ORAL	CAP DS PK	VRAYLAR	CARIPRAZINE HCL	V	Y
ORAL	CAPSULE	VRAYLAR	CARIPRAZINE HCL	V	Y
ORAL	TAB RAPDIS	CLOZAPINE ODT	CLOZAPINE	V	Y
ORAL	TAB RAPDIS	FAZACLO	CLOZAPINE	V	Y
ORAL	ORAL SUSP	VERSACLOZ	CLOZAPINE	V	Y
ORAL	TABLET	FANAPT	ILOPERIDONE	V	Y
ORAL	TABLET	LATUDA	LURASIDONE HCL	V	Y
ORAL	TAB RAPDIS	OLANZAPINE ODT	OLANZAPINE	V	Y
ORAL	TAB RAPDIS	ZYPREXA ZYDIS	OLANZAPINE	V	Y
ORAL	TAB ER 24	PALIPERIDONE ER	PALIPERIDONE	V	Y
ORAL	TAB ER 24	INVEGA	PALIPERIDONE	V	Y
ORAL	TABLET	NUPLAZID	PIMAVANSERIN	V	Y
ORAL	TAB ER 24H	SEROQUEL XR	QUETIAPINE FUMARATE	V	Y
ORAL	TAB RAPDIS	RISPERDAL M-TAB	RISPERIDONE	V	Y
ORAL	TAB RAPDIS	RISPERIDONE ODT	RISPERIDONE	V	Y
ORAL	CAPSULE	GEODON	ZIPRASIDONE HCL	V	Y
ORAL	CAPSULE	ZIPRASIDONE HCL	ZIPRASIDONE HCL	V	Y

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

NUPLAZID™ (pimavanserin) tablets, for oral use
Initial U.S. Approval: 2016

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.**
- **NUPLAZID is not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis. (5.1)**

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

NUPLAZID is an atypical antipsychotic indicated for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis. (1)

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

- Recommended dose is 34 mg, taken orally as two 17 mg tablets once daily, without titration. (2)
- Can be taken with or without food. (2)

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

Tablets: 17 mg. (3)

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

None. (4)

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

- QT Interval Prolongation: Increases in QT interval; avoid use with drugs that also increase the QT interval and in patients with risk factors for prolonged QT interval. (5.2)

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

Most common adverse reactions (≥5% and twice the rate of placebo): peripheral edema and confusional state. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact ACADIA Pharmaceuticals Inc. at 1-844-422-2342 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Strong CYP3A4 Inhibitors (e.g., ketoconazole): Reduce NUPLAZID dose by one-half. (2.2, 7.1)
- Strong CYP3A4 Inducers: Monitor for reduced efficacy. Increase in NUPLAZID dosage may be needed. (2.2, 7.1)

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

- Renal Impairment: No dosage adjustment for NUPLAZID is needed in patients with mild to moderate renal impairment. Use of NUPLAZID is not recommended in patients with severe renal impairment. (8.6)
- Hepatic Impairment: Use of NUPLAZID is not recommended in patients with hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 04/2016

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		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the treatment for hallucinations and/or delusions associated with Parkinson's disease?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. 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
4. Has withdrawal or reduction of the triggering medication resolved symptoms?	**Yes:** Pass to RPh; Deny; medical appropriateness	**No:** Go to #5
5. Is the patient on a concomitant first- or second-generation antipsychotic drug?	**Yes:** Pass to RPh; Deny; medical appropriateness	**No:** Go to #6

Approval Criteria		
6. 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

P&T Review: *01/2017*
Implementation: *TBD*

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

New Drug Evaluation: lifitegrast solution, ophthalmic

Date of Review: January 2017
Generic Name: lifitegrast
PDL Class: Not applicable

End Date of Literature Search: November 2016
Brand Name (Manufacturer): Xiidra™ (Shire US Inc.)
AMCP Dossier Received: Yes

Research Questions:

- Is there evidence that lifitegrast improves outcomes in patients with dry eye disease (DED), including improvement in symptoms of discomfort (as measured by patient symptom scores) and visual disturbance? If so, how does efficacy compare to other agents approved by the FDA for dry eye?
- Is there evidence that lifitegrast is safe in patients with DED? How do harms compare to other agents approved by the FDA for dry eye?
- Are there subpopulations of patients, such as those with Medicaid coverage, with DED that may benefit or experience more harms when treated with lifitegrast?

Conclusions:

- The U.S. Food and Drug Administration (FDA) approval of lifitegrast is based from three phase 3, double-blind, randomized controlled trials (OPUS – 1, 2, and 3) in patients with moderate to severe DED.[1, 2, 3] All studies were 12 weeks in duration and primary endpoints were assessed at that time. The majority of patients were white women, mean age of 59 years, with moderate DED symptoms. Small changes in primary endpoints between lifitegrast and placebo suggest no clinical benefit. Extensive exclusion criteria that include common conditions associated with DED limit the applicability of these findings to most patients.
- There is low quality and inconsistent evidence that lifitegrast may reduce inferior corneal staining scores (ICSS) (indicator of ocular surface damage, scores ranging from 0-4, 0 = none and 4 = confluent). Lifitegrast reduced ICSS from baseline by -0.75 compared to placebo +0.16 (mean difference [MD] 0.41; no confidence interval [CI] reported; p=0.0007) in one trial and by -0.73 compared to -0.71 with placebo (MD 0.02; no CI reported; p=0.6186) in a second trial.[1,2] Meaningful clinical changes in corneal staining scores have not been determined and the sensitivity of this test to detect differences is considered low.[4] ICSS scores have not been shown to be indicative of DED symptoms.
- There is low quality evidence that lifitegrast may decrease eye dryness scores (EDS).[2] The EDS visual analog scale (VAS) ranges from 0-100 (100 = maximal discomfort.[5] No minimally clinically important difference has been identified.[5]Lifitegrast decreased scores by -35.30 compared to -22.75 with placebo (MD 12.61; 95% CI, 8.51 to 16.70; p<0.0001).[2] A second study found lifitegrast decreased EDS by -37.9 points compared to -30.7 points for placebo (MD 7.16; 95% CI, 3.04 to 11.28; p=0.0007).[3] Such small mean differences between lifitegrast and placebo suggest changes may not be clinically meaningful.
- The most commonly occurring adverse reactions associated with lifitegrast use were eye irritation after installation, dysgeusia and reduced visual acuity. Early discontinuations were 3% higher in patients treated with lifitegrast compared to placebo (12% vs. 9%, respectively).[6]
- There is insufficient comparative evidence between lifitegrast and other treatments for DED and in subpopulations of patients with DED.

Recommendations:

- Restrict coverage of lifitegrast ophthalmic solution subject to prior authorization. Dry eye disease is not funded by the Oregon Health Plan (OHP).

Background:

It is estimated that over 20 million people in the United States have DED with estimated prevalence rates ranging anywhere from 5% to over 50%.[5] The cause of DED is not known but it is more common in the elderly and in post-menopausal women.[3] Dry eye disease results from disturbance of tear production and changes to the ocular surface that can cause visual disturbances and eye discomfort.[7] Dry eye disease is also known as keratoconjunctivitis sicca, dry eye syndrome and dysfunctional tear syndrome.[7] Symptoms associated with DED include burning, stinging, grittiness, itching and sometimes pain. Classification of DED is categorized as aqueous deficient or evaporative, with the potential for both conditions to occur concomitantly. Risk factors for DED include advanced age, female gender, poorer self-rated health, antidepressant or oral steroid use and Asian heritage.[5] Certain medical conditions are also known to increase the risk for DED:

- Diabetes mellitus
- Sjögren Syndrome
- Untreated thyroid disease
- Systemic inflammatory disease (e.g., graft-versus-host disease, rheumatoid arthritis, systemic lupus erythematosus, scleroderma)
- Lymphoma
- Sarcoidosis
- Chronic viral infections (e.g., hepatitis C, human immunodeficiency virus)
- Ocular surgery

A clinical practice guideline published by the American Academy of Ophthalmology recommends a comprehensive medical history and physical exam to determine if DED is present. Tear function, tear composition, and ocular surface alternations are evaluated to determine DED severity. Diagnosis of DED usually corresponds with 5 characteristics: 1) symptoms of discomfort 2) visual disturbance 3) tear film instability (potential for ocular surface damage) 4) increased osmolarity of tear film and 5) inflammation of the ocular surface.[5] Multiple tests have been used in the diagnosis of DED; however, clinical applicability and significance is unknown. Testing procedures, usually done by ophthalmologist, to aid in the diagnosis of dry eye are:

Schirmer's Test - The Schirmer tear test is used to determine tear section rate. Normal values of the Schirmer 1 test (anesthetic not used) are values greater than 10mm, with dry eye cutoff of 5 mm. This test is used to aid in the diagnosis of DED but is not considered a primary method.[8]

Ocular Surface Staining – Fluorescein staining is used to visualize the corneal surface. DED is associated with increased staining; however, there is low correlation to symptoms of dry eye.[9]

Ora Calibra Corneal and Conjunctival Staining score – Used to evaluate ocular surface staining (described above). Ora Calibra and Conjunctival Staining score is a validated scoring system with scores ranging from 0-4 (0 = none and 4 = confluent).[1] Each area is graded separately. The five areas are inferior, superior, central regions (relative to the cornea), temporal and nasal regions (relative to the conjunctiva). The inferior corneal staining score (ICSS) absorbs the most stain due to increased exposure to the environment.[10]

Tear Film Breakup Time (TFBUT) - The non-invasive tear film break-up time has been recommended as a test with moderately high sensitivity for diagnosing and monitoring DED.[5] Fluorescein is often used to visualize tear film since tear film instability is associated with DED if values are less than 5 seconds and may be a result of DED if less than 10 seconds; however, ocular surface damage does not always occur in DED and the sensitivity of this test to detect changes is considered low.[4,5]

Symptomatic tear-film break up time (SBUT) – The time between blinks when the patient is asked to stare is measured. Patients with dry eye have less corneal sensitivity and exhibit extended times between blinking.[11]

Outcomes used in the study of DED are not standardized and objective measurements do not consistently correlate with symptom severity.[5] Subjective assessment of DED is done by the use of questionnaires and is most indicative of efficacy of treatments. Patient assessment questionnaires that have been used in clinical trials are: McMonnies, Ocular Surface Disease Index (OSDI), Standard Patient Evaluation of Eye Dryness (SPEED), Symptom Assessment in Dry Eye survey (SANDE), Impact of Dry Eye on Everyday Life (IDEEL), Eye Dryness Score (EDS) and the Dry Eye Questionnaire (DEQ-5) (Table 1).[5] Minimum clinically important differences (MCID) in most questionnaires have not been established.

Table 1. Dry Eye Symptom Questionnaires[1,8,12]

Questionnaire	Scoring	Description
McMonnies	14 questions with an index score of 0-45 (higher scores associated with dry eye). Scores >14.5 are recommended for DED diagnosis.	Gender, age, dry eye symptoms, previous treatments, secondary symptoms, medical conditions associated with DED, dryness of mucous membranes and medication use are assessed.
Ocular Surface Disease Index (OSDI)	Scores range from 0-100 with higher scores indicating more severity. Normal range (0-12 points), mild dry eye (13-22 points), moderate dry eye (23-32 points) and severe dry eye (33-100 points). Suggested minimally clinically important difference is a 7.0 to 9.9 when applied to the total score of up to 100 or 4.5-7.3 points for mild to moderate DED or 7.3 to 13.4 points for severe DED.	The OSDI assesses symptoms and vision-related functioning. The OSDI consists of 12 questions related to the following subscales: symptoms, visual-related function (VR-OSDI), and environmental triggers. The subscales are a composite of mean scores ranging from 0-4, with 0 indicating symptoms none of the time and 4 indicating symptoms all the time.
Standard Patient Evaluation of Eye Dryness Questionnaire (SPEED)	Not applicable.	Types of symptoms, time frame, frequency and eye drop use are assessed.
Symptom Assessment in Dry Eye (SANDE)	Uses a 100 mm visual analog scale (VAS).	Quantifies frequency and severity of DED symptoms.
Impact of Dry Eye on Everyday Life (IDEEL)	20-item IDEEL-symptom bother module reports a clinically meaningful difference of 12 points.	Impact of DED on quality of life and daily living.
Eye Dryness Score (EDS)	The scores range from 0 (no discomfort) to 100 (maximal discomfort). No minimally clinically important difference has been identified.	The EDS is used to quantify patient discomfort based on a VAS.
Dry Eye Questionnaire (DEQ-5)	Scores of >6 indicate DED and scores >12 suggest Sjögren Syndrome.	Assesses frequency of watery eyes, discomfort, dryness, and late day intensity of discomfort and dryness.

There is no cure for DED. Management of dry eye depends on the severity level. Avoiding medications, such as systemic antihistamines and anticholinergics, which may cause or aggravate DED can be helpful. In patients with moderate to severe DED, artificial tears, anti-inflammatories (topical glucocorticoids), corticosteroids, topical cyclosporine (Restasis 0.05%) and punctal plugs can be considered.[8,13] Artifical tears is considered first-line treatment for dry eye.[7] Lifitegrast and cyclosporine ophthalmic preparations require a prescription for use.[6] Lifitegrast prevents the pro-inflammatory process associated with DED by targeting cytokines which block binding of lymphocyte function-associated antigen-1 (LFA-1). LFA-1 is a cell surface protein found on leukocytes which interacts with other molecules to produce an immune response. Topical cyclosporine helps to increase tear production.[14] Studies of ophthalmic cyclosporine showed the drug increased tear production by about 10% increase.[14]

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

Clinical Efficacy:
Lifitegrast ophthalmic 5% solution is used for the treatment of dry eye symptoms. The approved dosage is to instill 1 drop twice daily.[6] Lifitegrast was studied in two phase 3 trials (OPUS-1 and OPUS-2); but due to lack of consistency in findings and failure to meet co-primary endpoints, the FDA required a third phase 3 study (Table 3).[1,2,3] This study has not been published but data available from the FDA will be presented.[3]

OPUS-1
Patients over the age of 18 years with a history of bilateral dry eye were randomized to lifitegrast 5.0% or placebo given as 1 drop in each eye twice daily.[1] Patients satisfying initial screening were subjected to acute environmental stress (standardized temperature, humidity, air-flow, ambient light, and visual-tasking). To be included in the study, patients had to have worsening in inferior corneal fluorescein staining and ocular discomfort score (ODS). Subjects without worsening scores were excluded. One eye was designated to be enrolled in the study based on specified criteria. If both eyes qualified then the right eye would be the eligible study eye. Patients included in the study were a mean age of 61 years, predominately female (76%), 93% white, and they had moderate DED as indicated by a baseline ocular surface disease index OSDI score of 26. The primary outcome was change in inferior corneal staining lesions from baseline at 12 weeks, which has been shown to have a low correlation to symptoms.[1] Key secondary outcomes were changes in visual-related function subscale score of the Ocular Surface Disease Index (VR-OSDI) from baseline. The VR-OSDI measures vision related functions from 0 (none of the time) to 4 (all of the time). Study assessments were performed on days 14, 42 and 84. Results were analyzed on the modified intention-to-treat (mITT) population, using last observation carried forward (LOCF) for missing data. Lifitegrast reduced inferior corneal staining by -0.75 compared to placebo treated patients which increased by 0.16 (p=0.0007) (CI not provided). Numeric results were not provided for the visual related (VR) OSDI but changes from baseline for lifitegrast and placebo were not significantly different (p=0.7894). There were also 6 VAS subjective supportive endpoints that were evaluated and eye dryness was the only one that was found to be significantly less with lifitegrast compared to placebo (40.2% vs.41.6%); however, this is not clinically significant.[1] This endpoint was then used as a co-primary endpoint in future studies. Using corneal staining scores as a primary endpoint is limited because it is not considered a sensitive measure and does not correlate with dry eye symptoms. Limitations to the data include outcomes studied, a short term study of mostly white female patients and high level of reporting bias. There was also a chance for selection bias due to poor concealment of allocation procedures.

OPUS-2
Adult patients were randomized to lifitegrast 5.0% or placebo in a phase 3, randomized, double-blind controlled trial lasting 12 weeks.[2] Patients entered a 14-day screening period before randomization. During screening exams at day -14 and day 0, the eye which tested the worse on the ICSS was designated the study

eye. This was most likely done because it would be easier to show a benefit in an eye that has worse test scores. After randomization, patients were assessed at day 14, 42 and 84. Patients included in the study were a mean age of 59 years, 77% were female, current users of artificial tears, self-reported DED and had moderate to severe DED as measured by the eye dryness score. Sixty-six percent of placebo treated patients and 65% of lifitegrast patients had baseline eye dryness scores of ≥ 60 at baseline. The co-primary endpoints were the changes in eye dryness score, measured by VAS in both eyes (questionnaire used not specified), and inferior corneal fluorescein staining score from the designated eye.[2] The VAS is a 7 item patient reported symptom scale ranging from 0-100, with 0 = no discomfort and 100 = maximal discomfort. A secondary outcome was change in ocular discomfort score (scale of 0-4, with 0 = no discomfort, 4 = severe discomfort) in the designated study eye.

The first co-primary endpoint, change in eye dryness score, was improved by -35.30 in the lifitegrast group compared to -22.75 in the placebo group (TE [treatment effect] 12.61; 95% CI, 8.51 to 16.70; p<0.0001). The second co-primary endpoint, ICSS in designated eye, was similar for lifitegrast and placebo (-0.73 and -0.71, respectively). The ocular discomfort score was improved by -0.91 in the lifitegrast group versus -0.57 in the placebo group (TE 0.34; 95% CI, 0.15 to 0.53; p=0.0005). Lifitegrast was more effective than placebo at decreasing the mean eye discomfort score (-26.46 and -16.73, respectively) (p<0.0001).[2] The co-primary outcomes ICSS and change in eye dryness score are limited by the unknown clinical significance of these tests. This study has the potential for selection bias since patients included into the study had to have a positive response to eye dryness by VAS to be enrolled and details of VAS questionnaire were not provided. Patients were self-diagnosed with DED which was not confirmed by a provider. The study was of short duration which limits applicability to a chronic eye condition. The study results would have the most applicability to white women.

OPUS-3 (unpublished; FDA analysis)
In a third phase 3 trial required by the FDA, lifitegrast 5.0% was compared to placebo in 711 patients in a randomized, double-blind fashion.[3] Patients were a mean age of 59 years, 75% female and 75% white. Most patients had an ICSS score greater than 1.5 and an eye dryness score greater than 60. The use of artificial tears within 30 days of study randomization was required. Patients had to be willing to suspend artificial tear use during the study, which suggests the symptoms of dry eye were not severe The primary endpoint was change in EDS, as assessed by VAS, from baseline at day 84. Key secondary endpoints were changes in EDS at day 14 and day 42. At day 84 the EDS decreased by 37.9 with lifitegrast compared to 30.7 with placebo (mean difference 7.16 points; 95% CI, 3.04 to 11.28; p=0.0007).[3] Lifitegrast was also associated with greater improvements in EDS compared to placebo at day 14 and 42 (p<0.0001 for both comparisons).[3] Limited details on study design provided by the FDA made assessment of bias incomplete. Prohibited medications were used by 3.9% of patients taking lifitegrast and 3.1% of patients taking placebo and 3.2% of total population were randomized even though they failed to meet study inclusion or exclusion criteria. The small difference in EDS between lifitegrast and placebo of 7.16 points represents only a small change on a 100 point scale, which suggest results are not clinically significant. Extensive exclusion criteria limits external validity.

Clinical Safety:
Assessment of safety for lifitegrast is limited because the short duration of clinical trials; however, one safety study was conducted for 12 months. The most commonly occurring adverse reactions were irritation due to installation, dysgeusia and reduced visual acuity.[6] Other adverse reactions occurring in 1-5% of patients were the following: blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.[6] In the 12-month safety study, lifitegrast was associated with withdrawal due to adverse events in 12.3% compared to 9.0% of placebo treated patients.[15] Adverse events were similar to short term trials with no severe adverse reactions in either group.

Pharmacology and Pharmacokinetic Properties:

Table 2. Pharmacology of Lifitegrast.

Parameter	
Mechanism of Action	Lymphocyte function-associated antigen-1 (LFA-1) antagonist[6]
Absorption	NA
Distribution and Protein Binding	NA
Metabolism	NA
Half-Life	NA
Elimination	NA

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Ocular symptoms
2) Visual disturbances

Primary Study Endpoint:
1) ICSS change from baseline
2) EDS change from baseline

Table 3. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. OPUS-1[1] RCT, DB, PC, PG, MC	1. Lifitegrast 5.0% solution 1 drop BID (L) 2. Placebo 1 drop BID (P) Duration: 12 weeks	Demographics: Age: 61 years Male: 24% White: 93% Cataract hx: 52% ICSS: 1.83 OSDI score: 26 Key Inclusion Criteria: • Age ≥18 years • bilateral dry eye disease • use of or desire to use artificial tears in previous 6 mo. • Conjunctival redness • Corneal fluorescein staining score of ≥2.0 • STT of ≥1 to ≤10 • Best-corrected visual acuity of ≥0.7 logarithm Key Exclusion Criteria: • Ocular inflammation • Ocular infection • Ocular surgery within 12 months • Contacts • Pregnancy	mITT: L: 293 P: 295 Attrition: L: 4% P: 4%	Primary Endpoint: Change from baseline in inferior corneal staining score: L: -0.75 P: 0.16 MD 0.91 (CI not reported) p=0.0007	NA	D/C due to Adverse Events: L: 10 (3.4%) P: 3 (1%) p=NR Instillation Site Irritation: L: 69 (24%) P: 12 (4%) p=NR Instillation Site Pain: L: 63 (22%) P: 11 (4%) p=NR	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (high) randomized 1:1 by unmasked independent statistician. There were 5% more males in the placebo group than the lifitegrast group and 4% more patient in the placebo group with history of cataracts compared to the lifiterast group. Performance Bias: (low) packaging of active and placebo treatments were identical. All study personnel and patients were masked to treatment assignment. Detection Bias: (unclear) blinding of outcome assessors was not described. Attrition Bias: (low) ITT with LOCF used for analysis. Low attrition rate in both groups. Reporting Bias: (high) all pre-specified endpoints reported but results and CI not provided. The study was funded by the manufacturer. **Applicability**: Patient: only applies to patients with DED and no other inflammatory eye conditions. Not all patients with DED have corneal lesions but this was required for study enrollment. ODSI score of 26 at baseline suggests moderate DED. Use of artificial tears had to be discontinued 72 hours prior to visit 1. Intervention: dosage appropriate according to FDA labeling. Comparator: placebo comparison appropriate to assess efficacy. Outcomes: primary endpoint does not always correlate with dry eye symptoms. Setting: 13 US sites.

2. OPUS-2[2] RCT, DB, PC, PG, MC	1. Lifitegrast 5.0% solution 1 drop BID (L) 2. Placebo 1 drop BID (P) Duration: 12 weeks	Demographics: Age: 59 years Male: 23% White: 85% Cataract hx: 35% ICSS: 2.40 Eye dryness score: 69 Key Inclusion Criteria: • Age ≥18 years • self-reported dry eye disease • artificial tear use within the previous 30 days • Corneal fluorescein staining score of ≥2.0 in ≥1 eye region • Conjunctival redness eye score ≥1 in ≥1 eye region • Eye dryness score ≥40 and positive response in >1 eye • Best-corrected visual acuity of >0.7 logarithm Key Exclusion Criteria: • Systemic or ocular steroid use • Immuno-deficient/ suppressed • Ocular inflammation • Ocular infection • Pregnancy • Topical cyclosporine • Ophthalmic meds • Aspirin or antihistamine use • LASIK last 12 months • Contact lens use	mITT: L: 358 P: 360 Attrition: L: 10% P: 3%	Co-Primary Endpoints: Change from baseline in EDS (VAS) in both eyes: L: -35.30 P: -22.75 MD 12.61 (95% CI, 8.51 to 16.70; p<0.0001) ICSS in designated eye: L: -0.73 P: -0.71 MD 0.03 (95% CI, -0.10 to 0.17; p=0.6186) Secondary Endpoint: Ocular Discomfort Score (study eye only): L: -0.91 P: -0.57 MD 0.34 (95% CI, 0.15 to 0.53; p=0.0005) Eye Discomfort Score (both eyes)*: L: -26.46 P: -16.73 MD 9.77 (95% CI, 5.27 to 14.28; p<0.0001) * The eye discomfort score is measured by VAS and reported as a single score for both eyes. The EDS score used the same scoring system but may have been comprised of different terms but methodology was not described.	NA NA NA NA	D/C due to Adverse Events: L: 26 (7.3%) P: 3 (0.83%) p=NR Instillation Site Irritation: L: 11 (3.1%) P: 1 (0.3%) p=NR Instillation Site Pain: L: 5 (1.4%) P: 1 (0.3%) p=NR	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (high) randomized 1:1 by interactive web response system. There were 6% more females in the lifitegrast group compared to placebo. Performance Bias: (low) packaging of active and placebo treatments were identical. All study personnel and patients were masked to treatment assignment. Detection Bias: (unclear) outcome assessment was not described. Attrition Bias: (low) mITT with LOCF used for analysis. Low attrition rate in both groups. Reporting Bias: (low) all pre-specified endpoints reported. Study was funded by the manufacturer. **Applicability**: Patient: patients had to respond to placebo treatment in screening phase to be included. Patients were self-diagnosed with DED and had used artificial tears. Extensive exclusion criteria, including conditions associated with DED, limits applicability to most patients. Intervention: dosage appropriate based on FDA labeling. Comparator: placebo comparison appropriate to assess efficacy. Outcomes: eye dryness score and ICSS commonly used in ophthalmic studies but clinically meaningful changes have not been identified. Outcome methodology was not clear. Setting: Thirty US sites.

3. OPUS-3[3] RCT, DB, PC, PG, MC	1. Lifitegrast 5.0% solution 1 drop BID (L) 2. Placebo 1 drop BID (P) Duration: 12 weeks	Demographics: Age: 58 years Male: 24% White: 77% Key Inclusion Criteria: See OPUS-1 Key Exclusion Criteria: See OPUS-2	mITT: L: 355 P: 356 Attrition: L: 10% P: 10%	Primary Endpoints: Change from baseline in EDS: L: -37.9 P: -30.7 TE 7.16 (95% CI, 3.04 to 11.28; p=0.0007) Secondary Endpoint: Change from baseline in EDS at day 42: L: -33.2 P: -23.9 MD 9.32 (95% CI, 5.44 to 13.20; p<0.0001) Change from baseline EDS at day 14: L: -22.9 P: -15.0 MD 7.85 (95% CI, 4.33 to 11.37; p<0.0001)	NA NA NA	D/C due to Adverse Events: L: 22 (6.2%) P: 9 (2.5%) p=NR Instillation Site Irritation: L: 65 (18.2%) P: 11 (3.1%) p=NR Instillation Site Pain: L: 8 (2.2%) P: 0 p=NR	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (unclear) randomization not reported. Performance Bias: (unclear) no details on masking of drug allocation or physician and patient blinding. Detection Bias: (unclear) outcome assessment was not described. Attrition Bias: (low) mITT with LOCF used for analysis. Low attrition rate in both groups. Reporting Bias: (low) pre-specified endpoints reported. Study funded by the manufacturer. **Applicability**: Patient: majority of patients had an inferior corneal staining score of >1.5 and an eye dryness score of ≥60. Patients were users of artificial tears at study entry but willing to suspend treatment while in study, suggesting moderate symptoms. Extensive exclusion criteria, including conditions associated with DED, limits applicability to most patients. Intervention: dosage appropriate based on FDA labeling. Comparator: placebo comparison appropriate to assess efficacy. Outcomes: eye dryness score commonly used in ophthalmic studies but clinically meaningful changes have not been identified. Setting: Forty-two US sites.

Abbreviations [alphabetical order]: ARR = absolute risk reduction; BID = twice daily; CI = confidence interval; DED = dry eye disease; EDS = eye dryness score (ranges from 0-100, higher scores indicating more eye discomfort); ICSS = inferior corneal staining score; ITT = intention to treat; MD = mean difference; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; OSDI = Ocular Surface Disease Index; PP = per protocol; STT = Schirmer's tear test; TE = treatment effect; VAS = visual analog scale used in EDS; VR-OSDI = visual-related function subscale score of the Ocular Surface Disease Index (range 0-4).

References:

1. Sheppard JD, Torkildsen GL, Lonsdale JD, et al. Lifitegrast ophthalmic solution 5.0% for treatment of dry eye disease: results of the OPUS-1 phase 3 study. *Ophthalmology*. 2014;121(2):475-483. doi:10.1016/j.ophtha.2013.09.015.
2. Tauber J, Karpecki P, Latkany R, et al. Lifitegrast ophthalmic solution 5.0% versus placebo for treatment of dry eye disease: results of the randomized phase III OPUS-2 study. *Ophthalmology*. 2015;122(12):2423-2431. doi:10.1016/j.ophtha.2015.08.001.
3. Food and Drug Administration. Xiidra (lifitegrast opthalmic solution) Medical Review. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208073Orig1s000MedR.pdf. Published June 24, 2015. Accessed September 14, 2016.
4. Savini G, Prabhawasat P, Kojima T, Grueterich M, Espana E, Goto E. The challenge of dry eye diagnosis. *Clin Ophthalmol*. 2008;2(1):31-55.
5. Chao W, Belmonte C, Benitez del Castillo JM, et al. Report of the inaugural meeting of the TFOS i2 = initiating innovation Series: targeting the unmet need for dry eye treatment. *The Ocular Surface*. 2016;14(2):264-316. doi:10.1016/j.jtos.2015.11.003.
6. Xiidra (lifitegrast ophthalmic solution) [Prescribing Information]. Lexington, MA: Shire US Inc. June 2016.
7. Shtein R. Dry Eyes - UpToDate. *UpToDate*. December 22, 2015. Accessed November September 14, 2016.
8. Foulks G, Forstot L, Donshik P, et al. Clinical guidelines for management of dry eye associated with SjÖgren Disease. *Ocular Surface*. 2015;13(2):118-132.
9. Abelson MB, Holly FJ. A tentative mechanism for inferior punctate keratopathy. *Am J Ophthalmol*. 1977;83(6):866-869.
10. Ousler GW, Abelson MB, Nally LA, et al. Evaluation of the time to “natural compensation” in normal and dry eye subject populations during exposure to a controlled adverse environment. *Adv Exp Med Biol*. 2002;506(Pt B):1057-1063.
11. Abelson MB, Welch D, Netwig B. Symptomatic break-up time (SBUT) in dry eye patients with normal vs. low corneal sensitivity. *Investigative Ophthalmology and Visual Science*. 2009;13.
12. Miller KL, Walt JG, Mink DR, et al. Minimal clinically important difference for the ocular surface disease index. *Arch Ophthalmol*. 2010;128(1):94-101. doi:10.1001/archophthalmol.2009.356.
13. American Academy of Ophthalmology. Dry eye syndrome summary benchmark - 2015. American Academy of Ophthalmology. http://www.aao.org/summary-benchmark-detail/dry-eye-syndrome-summary-benchmark--october-2012. Published November 1, 2015. Accessed September 15, 2016.
14. Restasis (cyclosporine ophthalmic emulsion) [Prescribing Information]. Irvine, CA: Allergan, Inc. June 2013.
15. Donnenfeld ED, Karpecki PM, Majmudar PA, et al. Safety of Lifitegrast Ophthalmic Solution 5.0% in Patients With Dry Eye Disease: A 1-Year, Multicenter, Randomized, Placebo-Controlled Study. *Cornea*. 2016;35(6):741-748. doi:10.1097/ICO.0000000000000803.

Appendix 1: Highlights of Prescribing Information

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

XIIDRA™ (lifitegrast ophthalmic solution) 5%, for topical ophthalmic use
Initial U.S. Approval: 2016

----------INDICATIONS AND USAGE----------
Xiidra (lifitegrast ophthalmic solution) 5% is a lymphocyte function-associated antigen-1 (LFA-1) antagonist indicated for the treatment of the signs and symptoms of dry eye disease (DED). (1)

----------DOSAGE AND ADMINISTRATION----------
One drop twice daily in each eye (approximately 12 hours apart). (2)

----------DOSAGE FORMS AND STRENGTHS----------
Ophthalmic solution containing lifitegrast 5% (50 mg/mL). (3)

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

----------ADVERSE REACTIONS----------
The most common adverse reactions (incidence 5-25%) following the use of Xiidra were instillation site irritation, dysgeusia and decreased visual acuity. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Shire US Inc. at 1-800-828-2088 or FDA at 1-800-FDA-1088 or www.fda.gov./medwatch.

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

Revised: 06/2016