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, March 26, 2015 1:00 - 5:00 PM
Clackamas Community Training Center
29353 SW Town Center Loop East
Wilsonville, OR 97070

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
- A. Roll Call & Introductions — R. Citron (OSU)
- B. Conflict of Interest Declaration — R. Citron (OSU)
- C. Approval of Agenda and Minutes — B. Origer (Chair)
- D. Department Update — L. Saris (OHA)

II. PREFERRED DRUG LIST NEW BUSINESS
- A. Viekira Pak New Drug Evaluation — M. Herink (OSU)
  1. New Drug Evaluation
  2. Public comment
  3. Discussion of Clinical Recommendations to OHA
- B. Long-acting Opioids Class Update — A. Meeker (OSU)
  1. Class Update
  2. Public comment
  3. Discussion of Clinical Recommendations to OHA
- C. Drugs for Constipation Review — A. Gibler (OSU)
  1. Class Review
  2. Public comment
  3. Discussion of Clinical Recommendations to OHA
- D. Drug Class Scans — A. Gibler / M. Herink (OSU)
  1. Antiepileptic Drugs
  2. Topical Corticosteroids
  3. Public Comment
  4. Discussion of Clinical Recommendations to OHA

III. DUR NEW BUSINESS
- A. Fibromyalgia Drug Use Evaluation — A. Gibler / K. Ketchum (OSU)
  1. Literature Review
  2. Drug Use Evaluation
  3. Public Comment
  4. Discussion of Clinical Recommendations to OHA

B. PPI/H2RA Class Updates and Drug Use Evaluation — A. Gibler / K. Ketchum (OSU)
   1. Class Update
   2. Drug Use Evaluation
   3. Public Comment
   4. Discussion of Clinical Recommendations to OHA

C. High Dose Opioid Policy Evaluation — T. Williams (OSU)
   1. Policy Evaluation
   2. Discussion of Clinical Recommendations to OHA

IV. EXECUTIVE SESSION

V. RECONVENE for PUBLIC RECOMMENDATIONS

VI. ADJOURN

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Name	Title	Profession	Location	Term Expiration
William Origer, M.D.	Physician	Medical Director	Corvallis	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
Arturo Salazar, M.D.	Physician	Pediatric Internist	Eugene	December 2017
James Slater, Pharm.D.	Pharmacist	Pharmacy Director	Beaverton	December 2017
Dave Pass, M.D.	Physician	Medical Director	West Linn	December 2016
Stacy Ramirez, Pharm.D.	Pharmacist	Community Pharmacist	Albany	December 2016
Kathryn Lueken, M.D., M.M.M.	Physician	Medical Director	Salem	December 2016
Cathy Zehrung, R.Ph.	Pharmacist	Pharmacy Manager	Silverton	December 2015
Phil Levine, Ph.D.	Public	Retired	Lake Oswego	December 2015
Vacant	Physician			December 2015

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, January 29, 2015 1:00-5:00 PM
Wilsonville Training Center
29353 SW Town Center
Wilsonville, OR 97070

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: Cathy Zehrung, RPh; Phillip Levine, PhD; William Origer, MD; Kathryn Lueken, MD; James Slater, PharmD; Caryn Mickelson, PharmD; Stacy Ramirez, PharmD; Tracey Klein, PhD., FNP;

Members Present by Phone: David Pass, MD; Arturo Salazar, MD;

Staff Present: Kathy Ketchum, RPh, MPA:HA; Megan Herink PharmD, BCPS; Richard Holsapple, RPh; Roger Citron, RPh; Ted Williams, PharmD; Shannon Jasper; Linnea Saris; Amanda Meeker, PharmD; Andrew Gibler, PharmD; Dee Weston,

Staff Present by Phone: Kathy Sentena, PharmD;

Audience: Barry Benson (BMS), Leslie Mann (Celgene), Pat Wiseman (AstraZeneca), Bruce Smith (GlaxoSmithKline), Ann Marie Licos (AstraZeneca), Carrie Johnson (AstraZeneca), Mark Handley (AstraZeneca), Venus Holder (Lilly), Michelle Widolff (Lundbeck)*, Bill Ferguson (Lundbeck), Patrick Moty (Supennus), Margaret Olman (Daiichi Sankyo), Steve Hill (PSI), Paul Bonham (Novo), Becky McReynolds (Abbvie), Michelle Bice (Gilead), Georgette Dewilewski (Indivior), Steve Nemirow*, Pamela Vincent (Indivior), Meg Nguyen (Teva)*, Deron Grothe (Teva), Mary Kemhus (Navartis), Dean Haxby (OSU), Cynthia Patterson ()*, Sarah Day (RCG & Associates)*, Jenna Colabianchi, PharmD (Sunovian), Stuart O'Brochta (Gilead)*, Kim Blood (WVCH), Stacy Eria (FamilyCare), Bob Sneidker (Janssen)*, Jeannie Kenyon (Amgen), Mark Pledger (Novartis), Scott Larson (BMS), Kent Benner, MD (Oregon Clinic)*, Pat Trifinor (VBG), Lincoln Alexander (Student), Desiree Allen (Abbvie), Allen Hammagren (Abbvie), Lorren Sandt (Caring Ambassadors)*, Don Stecher (Novartis), BJ Cavnor (One in Four)*, Dr. Atif Zaman (OHSU)*, David Byram (Orexo US)*

(*) Provided verbal testimony

I. CALL TO ORDER

a. The meeting was called to order at approximately 1:00 pm. Introductions of Committee members and staff.

b. Election of Chair and Vice Chair for the P&T Committee.

Elected Dr. Bill Origer for Chair. Motion, Second, all in favor. Approved.
Elected Tracy Klein PhD., FNP elected for Vice Chair. Motion, Second, all in favor. Approved.

c. Mr. Citron reported there are no new conflicts of interest to declare.

d. Approval of agenda and minutes presented by Dr. Origer (pages 1 - 8)

ACTION: Approved as is.

e. Department updates presented by Linnea Saris.

II. DUR ACTIVITIES

a. Quarterly Utilization Reports (pages 9 - 13)
Presented by Mr. Citron.

b. ProDUR Report (pages 14 - 15)
Presented by Mr. Holsapple.

c. RetroDUR Report (pages 16 - 18)
Presented by Dr. Williams.

d. Oregon State Drug Reviews
Presented by Dr. Sentena.
   1. What's New with Oral Anticoagulants? (pages 19 - 21)
   2. Guidance Update for Prophylaxis of Respiratory Syncytial Virus (pages 22 – 24)

III. DUR NEW BUSINESS

a. Droxidopa (Northera™) (pages 25 - 40)
Dr. Gibler presented the following new drug evaluation:

   1. The committee requires prior authorization for patients limiting to the following:
      a. Treating diagnosis must be an OHP funded condition, **AND**
      b. Patient must have a diagnosis of symptomatic orthostatic hypotension due to primary autonomic failure, dopamine beta-hydoxylase deficiency, or non-diabetic autonomic neuropathy**, AND**
      c. Patient must not be currently receiving antihypertensive therapy, **AND**
      d. Patient must have a documented trial of appropriate therapy for orthostatic hypotension, including both fludrocortisone and midodrine, unless physician provides justification (e.g., contraindications, concern for adverse effects, etc.).

   2. For approval beyond 30 days, require documentation that:
      a. Patient must have a documented response to therapy (e.g., improvement in dizziness, lightheadedness, etc.).

   3. After evaluation presentation, the committee agreed to change initial approval from 1 month to 14 days, and each subsequent approval from 1 year to 3 months.

Public Comment:
Michelle Widolff from Lundbeck gave public comment.

ACTION: Motion, 2nd, All in Favor. Approved.

IV. PREFERRED DRUG LIST NEW BUSINESS

a. Hepatitis C Class Update and New Drug Evaluation (pages 41 - 72)
Dr. Herink presented the following update and new drug evaluation:

Dr. Zaman and Dr. Benner presented to the members and public the outcome from the Hepatitis C Advisory Group and the current recommendations.

1. Implement PA criteria to prioritize use so that patients defined by the AASLD guidelines as "highest priority" who are at high risk for liver-related complications and severe extrahepatic hepatitis are treated.

    a. Stage 3 or 4 fibrosis without decompensated cirrhosis, **OR**
    b. Those receiving an organ transplant, **OR**
    c. Patients with extrahepatic manifestations, including:
        i. Type 2 or 3 cryoglobulinemia with end-organ manifestations (e.g., vasculitis)
        ii. Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis.

2. Evaluate cost in executive session for PDL decision.

3. *After executive session, approved Harvoni (ledipasvir/ sofosbuvir) as a preferred product on the PDL. Amend PA criteria so Harvoni is preferred over Sovaldi for Genotypes 1 and 3. PA criteria effective as soon as supplemental rebate is in place.

Public Comment:
BJ Cavnor from One in Four gave public testimony.
Steve Nemirow self employed gave public testimony.
Lorren Sandt from Caring Embassadors gave public testimony.
Stuart O'Brochta from Gilead gave public testimony.
Bob Snediker from J&J gave public testimony.

***ACTION:** After executive session. All in favor. Approved.

b. Hypoglycemic Agents New Drug Evaluations (pages 73 - 135)
Dr. Sentena presented the following new drug evaluations:

1. Albiglutide (Tanzeum™) (pages 73 – 87)
    a. Add albiglutide to current PA criteria for GLP-1 analogs.
2. Dulaglutide (Trulicity™) (pages 88 – 102)
    a. Add dulaglutide to current PA criteria for GLP-1 analogs.
3. Empagliflozin (Jardiance) (pages 103 – 118)
    a. Add empagliflozin to current PA criteria for SGLT2s.
4. Canagliflozin / Metformin (Invokamet™) (pages 119 – 135)
    a. Add canagliflozin-metformin to current PA criteria for SGLT2s.
5. No changes to oral hypoglycemic PDL classes recommended at this time.

Public Comment:

Bob Snediker form J&J gave public comment.

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

c. Colony Stimulating Factor Class Updates (pages 136 – 152)
Ms. Ketchum presented the following class updates:

1. Consider a DUE of the Colony Stimulating Factors to assess adherence to NCCN* guidelines and Guideline Note 11 of the OHP List of Prioritized Services.
*National Comprehensive Cancer Network
2. Evaluate PDL placement of tbo-filgrastim after evaluating costs in executive session.
3. *After executive session, make Granix (tbo-filgrastim) preferred on the PDL.
4. *After executive session, no DUE necessary at this time.

Public Comment:
Meg Nguyen from Teva gave public comment.

***ACTION:** After executive session. All in favor. Approved.

d. Ophthalmic VEGF for Glaucoma Class Update (pages 153 – 161)
Dr. Herink presented the following class update:

1. Maintain pegaptanib and aflibercept as non-preferred due to lower strength of evidence.
2. Evaluate comparative costs in executive session.
3. * After executive session, no changes to the PDL.

***ACTION:** After executive session. All in favor. Approved.

e. Ophthalmic Drugs for Glaucoma Class Update (pages 162 – 179)
Dr. Gibler presented the following class update:

1. Maintain unoprostone and the brinzolamide / brimonidine fixed-combination product as non-preferred.
2. Continue to include a medication from each category on PDL, including miotics, alpha-adrenergic agonists, beta-blockers, carbonic anhydrase inhibitors, and prostaglandin analogs.
3. Evaluate comparative costs in executive session.
4. * After executive session, no changes to the PDL.

***ACTION:** After executive session. All in favor. Approved.

f. Opioid Dependence Class Update (pages 180 – 201)
Dr. Gibler presented the following class update:

1. No further research or review needed at this time.
2. Evaluate comparative costs in executive session.
3. * After executive session, no changes to the PDL.

Public Comment:
Pamela Vincent from Reckitt Benhiser gave public comment.
Cynthia Patterson from BioDelivery Sciences gave public comment.
David Byram from Orexo US gave public comment.

***ACTION:** After executive session. All in favor. Approved.

g. Olodaterol New Drug Evaluation (pages 202 – 212)
Dr. Meeker presented the following drug evaluation:

1. Designate olodaterol as non-preferred due to lack of quality evidence demonstrating clinical effectiveness.
2. Evaluate comparative costs in executive session.

***ACTION:** After executive session. All in favor. Approved.

h. Drug Class Scans

1. Ophthalmic Antibiotics (pages 213 – 218)
Dr. Meeker presented the following drug scan:

a. No further research or review needed at this time.
b. Evaluate comparative costs in executive session.
c. *After executive session, no changes to the PDL.

***ACTION:** After executive session. All in favor. Approved.

2. Ophthalmic Antibiotics / Corticosteroids (pages 219 – 220)
Dr. Meeker presented the following drug scan:

a. No further research or review needed at this time.
b. Evaluate comparative costs in executive session.
c. *After executive session, make gentamicin / prednisolone ophthalmic suspension and ointment preferred on PDL.
d. *After executive session, make Maxitrol (neomycin, polymyxin B, and dexamethasone) ophthalmic ointment preferred on PDL.

***ACTION:** After executive session. All in favor. Approved.

3. Cephalosporins (pages 221 – 227)
Dr. Gibler presented the following drug scan:

a. Maintain at least one oral agent from 1st, 2nd, and 3rd generation cephalosporins and amoxicillin / clavulanate, as well as age appropriate dosage formulations.
b. No further research or review needed at this time.
c. Evaluate comparative costs in executive session.
d. *After executive session, make cefuroxime oral suspension preferred on PDL.

***ACTION:** After executive session. All in favor. Approved.

4. Topical Psoriasis (pages 228 – 235)
Dr. Herink presented the following drug scan:

a. No further research or review needed at this time.
b. Evaluate comparative costs in executive session.
c. *After executive session, no changes to the PDL.

***ACTION:** After executive session. All in favor. Approved.

5. Drug Effectiveness Review Project (DERP) Scans:

a. ADHD (pages 236 – 254)

Dr. Gibler presented the following DERP scan:

1. No further research or review needed at this time.
2. Evaluate comparative costs in executive session.
3. *After executive session, no changes to the PDL.

***ACTION:** After executive session. All in favor. Approved.

b. ACE-Inhibitors, Angiotensin Receptor Blockers, Direct Renin Inhibitors (pages 255 – 295)
Dr. Gibler presented the following DERP scan:

1. No further research or review needed at this time.
2. Evaluate comparative costs in executive session.
3. *After executive session, no changes to the PDL.

Public Comment:
Sarah Day from Silvergate Pharmaceuticals gave public comment.

***ACTION:** After executive session. All in favor. Approved.

c. Statins (pages 296 – 360)
Dr. Gibler presented the following DERP scan:

1. No further research or review needed at this time.
2. Evaluate comparative costs in executive session.
3. *After executive session, no changes to the PDL.

***ACTION:** After executive session. All in favor. Approved.

d. Macrolides (pages 361 – 372)
Dr. Gibler presented the following DERP scan:

1. No further research or review needed at this time.
2. Evaluate comparative costs in executive session.
3. *After executive session, no changes to the PDL.

***ACTION:** After executive session. All in favor. Approved.

V. EXECUTIVE SESSION

VI. EXECUTIVE SESSION

VII. RECONVENE for PUBLIC RECOMMENDATIONS

VII. ADJOURN

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
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New Drug Evaluation: Ombitasvir, paritaprevir/ritonavir plus dasabuvir (Viekira Pak®)

Month/Year of Review: March 2015
Generic Name: Ombitasvir, paritaprevir/ritonavir plus dasabuvir
PDL Class: Hepatitis C agents

End Date of Literature Search: January 2015
Brand Name (Manufacturer): Viekira Pak® (Abbvie)
Dossier Received: Yes

Indication:
Ombitasvir, paritaprevir and ritonavir plus dasabuvir (OMB/PTV-R + DAS) is indicated for the treatment of patients with genotype 1 (GT1) chronic hepatitis C virus (HCV) infection including those with compensated cirrhosis. OMB/PTV-R +DAS is not recommended for use in patients with decompensated liver disease.[1]

Research Questions:
- Is OMB/PTV-R + DAS more effective than currently available alternative agents for the treatment of chronic hepatitis C (CHC) in achieving a sustained virologic response (SVR) and preventing long-term complications including hepatocellular carcinoma (HCC), liver-related morbidity, and mortality?
- Is OMB/PTV-R + DAS safer than other available agents for the treatment of CHC genotype 1 (GT1) in adults?
- What subgroups of patients will benefit most from treatment with OMB/PTV-R + DAS?

Conclusions:
- There is high quality evidence that in GT1 CHC patients with generally mild disease and favorable disease characteristics, treatment with OMB/PRB-R + DAS results in very high (87%-100%) SVR12 rates.
- Overall SVR12 rates ranged from 96-100% in treatment-experienced and treatment-naïve patients without cirrhosis. One exception was in patients with GT1a infection treated without ribavirin (RBV) who experienced an SVR of 90%. For patients infected with GT1b, adding RBV did not appear to improve SVR12 rates.
- Overall SVR12 rates in patients with cirrhosis ranged from 89-100%, with the lowest in GT1a patients treated for 12 weeks (89%). Extending treatment to 24 weeks in this population increased SVR12 rates to 95% (treatment difference 6%). The difference appears to be driven primarily by patients who were previous null responders; however numbers were small for all subgroups. The clinical significance of the difference in efficacy remains in question due to the small margin of improvement and increased cost and risk of ribavirin (RBV) and adverse events associated with doubling the treatment duration for all patients. There is a statistically higher rate of relapse with 12 weeks of treatment compared to 24 weeks (RR 9.9; 95% CI 1.7 to 59), based on low to moderate quality of evidence.
- There is very low quality evidence that a regimen with OMB/PTV-R + DAS may be effective in patients post-liver transplantation. This is based on a small (n=34) phase 2 trial in patients with stable liver disease. Patients with aggressive recurrence, decreased hepatic function, fibrosis, and decompensation were excluded and therefore the efficacy in this population remains unknown.

- Incidence of adverse events associated with OMB/PTV-R + DAS were low overall and there were very few discontinuations due to adverse events in clinical trials. The most common adverse events were fatigue, nausea, pruritus, other skin reactions, insomnia, and asthenia. Adverse events were more common in regimens that included RBV than those without RBV, as well as with the longer 24-week regimen. The most relevant adverse event related to treatment is a small risk of elevated post-baseline alanine aminotransferase (ALT) levels, though risk is much higher among females using systemic estrogen-containing products and it remains unknown which patients will require close monitoring. Treatment is not recommended for use in patients with moderate or severe hepatic impairment until more data are available.
- OMB/PTV-R + DAS has potential serious drug-drug interactions and patients should be assessed throughout therapy (see table 2 in appendix). Particularly, the co-administration of certain antiretroviral agents is not recommended with OMB/PTV-R + DAS and is of special consideration in patients with HCV/HIV co-infection.
- There is insufficient evidence to determine efficacy and safety in certain important subgroups including non-whites, patients 65 years of age and older, intravenous drug users, and patients with decompensated cirrhosis or advanced liver disease (Child-Pugh scores >6).
- There is insufficient comparative evidence evaluating long-term outcomes of OMB/PTV-R + DAS to other direct-acting antiviral agents.

Recommendation:

- Evaluate comparative costs in executive session for PDL decision-making.
- If OMB/PTV-R + DAS is cost-effective compared to other treatment options based on Medicaid costs, implement prior authorization criteria (Appendix 2) to prioritize use so that patients defined by the AASLD guidelines as "highest priority" who are at high risk for liver-related complications and severe extrahepatic hepatitis are treated. Limit use of OMB/PTV-R + DAS to the following patients (highest priority based on the AASLD guidelines) at this time:
    - Stage 3 and 4 fibrosis without decompensated cirrhosis
    - Those receiving an organ transplant
    - Patients with extrahepatic manifestations, including:
        - Type 2 or 3 cryoglobulinemia with end-organ manifestations (vasculitis)
        - Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis
    - Patients prescribed medication by or in consultation with a hepatologist or gastroenterologist with experience in Hepatitis C.
    - Approve for 12 weeks and limit a 24-week regimen to post-liver transplant patients or patients with Genotype 1a with cirrhosis who are previous null responders.
- Exclude patients from treatment who are receiving drug products containing ethinyl estradiol, those with decompensated liver disease, patients with HCV genotype 2,3,4,5 or 6 infection, and HIV/HCV co-infected patients not receiving suppressive antiretroviral therapy (who may be at increased risk of HIV-1 protease inhibitor drug resistance) OR with significant antiretroviral drug-interactions (efavirenz, darunavir/ritonavir, lopinavir/ritonavir, rilpivirine).

Background:

Chronic HCV is the leading cause of complications from chronic liver disease, including cirrhosis, liver failure, and hepatocellular carcinoma. It is also the leading indication for liver transplantation in the Western world.[2] The goal of treatment for CHC is to prevent these long-term health complications. However, it remains difficult to design long-term clinical trials that are large enough to provide direct evidence for these outcomes. The SVR rate is defined as the proportion of patients who experience a decline in HCV-RNA to undetectable levels following completion of antiviral treatment, as measured by a sensitive polymerase chain reaction assay. It is the standard marker of successful treatment in clinical trials and is associated with the long-term absence of viremia. There is some evidence of an association of achieving an SVR and reductions in mortality, liver failure, and cancer. [2] However, this evidence is from observational studies only and those with cirrhosis prior to treatment have been shown to still be at risk for hepatocellular carcinoma (HCC) during follow-up. The two major predictors of SVR are

viral genotype and the pretreatment viral load. Other factors associated with an increased likelihood of achieving an SVR include female sex, age less than 40 years, non-Black race, lower body weight, absence of insulin resistance, and absence of bridging fibrosis or cirrhosis on liver biopsy. Trials have historically used SVR at week 24 of follow-up (SVR24) as a primary endpoint. SVR 24 has been associated with improvements in quality of life and studies have demonstrated that SVR24 is associated with a decrease in decompensated liver disease, hepatocellular carcinoma, liver transplant, and all-cause mortality. More recent studies use SVR at week 12 of follow-up (SVR12) as the primary endpoint, based on evidence that the majority of patients who have an SVR at week 12 maintain it until week 24.[3] Relapse is defined as a patient achieving HCV RNA less than the lower limit of quantitation or the lower limit of detection at the last measurement on treatment but subsequently having a HCV RNA greater than or equal to the lower limit of quantitation or detection post-treatment.[4] In addition, genetic variation in both virus and host can affect treatment response.

Patients at greatest risk of progressing to cirrhosis have detectable HCV-RNA and liver histology demonstrating fibrosis (Metavir fibrosis stage 2 or greater). Patients with compensated cirrhosis are at risk of progressing to decompensation hepatocellular carcinoma, or death. The urgency of treating HCV should be based on the risk of developing decompensated cirrhosis or dying from liver-related disease, and prolonging graft survival in liver transplant recipients. Disease progression varies greatly among patients with compensated liver disease and the number needed to treat to prevent long term outcomes is dependent on the baseline risk for events. The newer costly treatments with high SVR rates will have the most benefit among patients at highest risk of cirrhosis-related events.[5]

In the United States, genotype 1 infection is found in around three-quarters of patients and is associated with a lower response to antiviral treatment than infection with genotypes 2 and 3, which are present in about 20% of patients. [2] Genotype 1 includes subgenotypes, of which 1a and 1b are the most common. Cure rates for genotype 1a and 1b infection may differ depending on the treatment regimen. Therapies to treat HCV infection have advanced significantly over the past several years. Prior to 2011, the combination of pegylated interferon and ribavirin (PEG/RBV) was the standard of care and approximately 55-60% of patients achieved a SVR. Severe adverse effects also limited the success of therapy. In 2011, the first generation direct acting antiviral protease inhibitors, boceprevir and telaprevir, were FDA approved.[6] Several randomized controlled trials (RCTs) showed improved SVR rates (63-79%) with triple therapy compared to PEG/RBV dual therapy. However, these agents still come with several safety concerns and still depend on combination therapy with PEG/RBV which can result in serious adverse reactions. With the recent development of interferon-free regimens, these therapies have gone out of favor.

In 2013, the second generation direct-acting antiviral agents (DAAs), simeprevir (SMV) and sofosbuvir (SOF) were approved.[3] Sofosbuvir and RBV, studied together for 24 weeks in those ineligible to receive interferon, was the first interferon-free therapy for the treatment of genotype 1 infection. These regimens decreased the duration of therapy, decreased adverse events, and again demonstrated improved rates of SVR. In addition, recent data from show real world discontinuation rates of SOF + PEG/RBV may be up to 5-times greater than rates seen in clinical trials. In late 2014, two additional interferon-free therapies that combine two or more DAAs have been studied, including LDV/SOF and the OMB/PTV-R + DAS regimen. However, these new drugs are expensive, and a significant challenge is identifying which patients will benefit most from receiving treatment, since only 5-20% of patients with chronic hepatitis C will develop cirrhosis over 20 years.[7] Viekira Pak includes: ombitasvir, a hepatitis C virus NS5A inhibitor; paritaprevir, a hepatitis C virus NS3/4A protease inhibitor; dasabuvir, a hepatitis C virus non-nucleoside NS5B palm polymerase inhibitor; and ritonavir, a potent CYP3A inhibitor that is not active against HCV but boosts concentrations of paritaprevir.[1] It is available as a fixed-dose combination of ombitasvir, paritaprevir, and ritonavir that is co-packaged in a fixed-dose tablet with dasabuvir.[8]

Studies including patients with decompensated cirrhosis, renal failure, or other comorbidities and minority racial and ethnic groups are lacking and these remain some of the most difficult patients to treat.[9]

Clinical Efficacy:

The FDA approval of OMB/PTV-R + DAS with or without RBV was primarily based on six published Phase 3 randomized, multi-center trials (details in evidence table).[8] Two of these trials were placebo-controlled to compare harms; efficacy results were non-comparative.[10,11] The remaining 4 trials were regimen-controlled designed to assess SVR rates with or without RBV in certain subgroup of patients (GT1a treatment-naïve and GT1b treatment-naïve and experienced).[12–14] All 6 clinical trials evaluated HCV genotype 1 patients with compensated liver disease with and without cirrhosis for treatment durations of 12 or 24 weeks. The primary efficacy endpoint was sustained viral response at 12 weeks post-treatment (SVR12) compared to a historical control rate of therapy with telaprevir Comparisons to historical data may be limited by the biased selection of patients given the controls are not randomized and important differences in patient populations may not be accounted for in the analysis. All pivotal trials were sponsored by Abbvie.

SAPPHIRE I was a phase 3, double-blind, placebo controlled RCT comparing OMB/PRB-R + DAS plus RBV to placebo for 12 weeks of treatment.[10] Subjects on placebo were administered open-label active study drug for 12 weeks following completion of the double-blind treatment period. All subjects were followed for 48 weeks post-treatment for safety and efficacy monitoring. The primary efficacy analyses assessed noninferiority and superiority with respect to SVR12 associated with the active regimen compared to a historical rate of 78% (95% CI, 75 to 80%), with a non-inferiority margin of 10.5%. This historical rate was based on rates among previously untreated patients without cirrhosis who received telaprevir and PEG/RBV from the REALIZE study. The SVR12 was 96.2% (95% CI, 94.5- 97.9%) overall in the treatment group and was both noninferior and superior to the historical control rate because the lower confidence bound exceeded 80%, achieving superiority. Rates were similar in all subgroups, including those with IL28B genotype, black patients (96.4%), fibrosis score, and baseline HCV RNA level. A total of 7 patients (1.5%) relapsed by post-treatment week 12.

SAPPHIRE-2 was a similarly designed trial evaluating 12 week of OMB/PTV-R + DAS plus RBV in treatment experienced (prior PEG/RBV dual therapy) GT1 patients, including relapsers (29%), previous partial responders (21.9%), and previous null response (49.2%).[11] Patients previously on triple therapy with a protease inhibitor were excluded and approximately 32% of patients had a Fibrosis score of F2 or F3. Overall, 96.3% of patients achieved an SVR after 12 weeks post treatment and rates were similar among subgroups. Seven (2.4%) of patients had a viral relapse, 6 of these being prior null responders. In general, patients from SAPPHIRE I AND II were relatively healthy with few patients with advanced disease. A limitation of both SAPPHIRE I and II is that neither reported efficacy data for the placebo group; however, the FDA analysis showed that viral load didn't change in the placebo group, as would be expected.

PEARL II was a poor-quality phase III, open-label study evaluating the efficacy and safety of OMB/PTV-R + DAS with or without RBV in noncirrhotic PEG/RBV treatment-experienced HCV genotype 1b patients, including null responders (34.9%), partial responders (28.5%), and relapsers (36.6%).[12] Overall, 96.5% in the group with RBV and 100% in the group without RBV achieved SVR12 (Treatment Difference 3.4%; 95% CI, -0.4-7.2%), both superior to the historical rate achieved with telaprevir. No patients from either group experienced relapse. SVR12 rates were slightly lower in group 1 null responders (93.5%). This study demonstrated no impact with RBV on SVR12 in treatment-experienced HCV GT1b patients.

Pearl III and Pearl IV were identically designed studies comparing OMB/PTV-R + DAS plus RBV for 12 weeks vs. without RBV in HCV treatment naïve patients without cirrhosis.[13] The only difference was Pearl III evaluated therapy in patients with genotype 1b infection, while PEARL IV studied those with genotype 1a infection. All patients received open-label OMB/PTV-R + DAS and either RBV twice daily or matching placebo. Patients and investigators were blinded to RBV treatment. The primary objective for both studies was to assess the noninferiority of each group compared with the historical rate with telaprevir triple therapy (72% with GT1a infection and 80% among genotype 1b infection) using a pre-specified noninferiority margin of 10.5%. Noninferiority of the group without RBV compared to treatment with RBV was also assessed. In Pearl IV (GT1a), both the group with RBV and without RBV were noninferior and superior to the historical rate. However, there was a significant difference between the two groups and the regimen without RBV did not meet the noninferiority criteria compared to treatment with RBV (90.2% vs. 97%; difference -6.8%; 95% CI -12 to -1.5%). In patients with GT1a infection, 18 patients had virologic failure, 16 of which were in

the regimen without RBV. In PEARL III (GT1b), both groups reached noninferiority and superiority compared to the historical rate and the group without RBV also reached nonferiority to the group with RBV in achieving SVR (99% vs. 99.5%; difference -.5%; 95% CI -2.1 to 1.1). Only one patient with GT1b infection had virologic failure.

TURQUOISE II compared 12 weeks of OMB/PTV-R + DAS plus RBV to 24 weeks of therapy in patients with HCV GT1 and compensated cirrhosis.[14] This included both treatment-naïve and treatment-experienced patients. Patients with evidence of decompensation were excluded from the study. Regimens were compared to the historical SVR24 rate for telaprevir (56% in treatment-naïve and 47% for treatment-experienced) in HCV GT1 patients with cirrhosis. Both groups were noninferior and superior to the historical rate with telaprevir plus PEG/RBV in patients with cirrhosis. There was no statistically significant difference in SVR12 between the 12-week and 24-week regimens (91.8% vs. 95.9%; p=0.09; RR 0.93; 95% CI, 0.86 to 1.0). Among patients with GT1a with a prior null response, only 80% of patients receiving 12 weeks of therapy achieved a SVR, compared to 92.0% in the 24-week group. Analysis showed that a prior null response to PEG/RBV (OR 0.39; 95% CI, 0.16-0.94), infection with subgenotype 1a (OR 0.12; 95% CI, 0.02-0.90), and former injection-drug use (OR 0.35; 95% CI, 0.14 to 0.86) were associated with a lower likelihood of SVR12. In addition, significantly more people in the 12-week group had a relapse than in the 24-week group (5.9% vs. 0.6%). Extending treatment to 24 weeks in this population increased SVR12 rates to 95% (treatment difference 6%). The difference appears to be driven primarily by patients who were previous null responders; however numbers were small for all subgroups. The clinical significance of the difference in efficacy remains difficult due to the small margin of improvement and increased cost and risk of RBV adverse events associated with doubling the treatment duration for all patients. Over half of patients who experienced a relapse had HCV genotype 1a and a prior null response to PEG/RBV treatment. Although this trial is important in evaluating treatment in more difficult to treat patients with cirrhosis, only patients with Child-A cirrhosis were included. Eligibility criteria allowed for inclusion of patients with low platelets or albumin, however; median platelet count was only slightly lower than the normal limit and median albumin was within normal range. Therefore, it is still unknown how patients with more advanced cirrhosis will respond to treatment with OMB/PTV-R + DAS.

The FDA approved length of therapy in GT1a with cirrhosis is 24 weeks and in patients with GT1b and cirrhosis, the FDA approved label is for 12 weeks of therapy. However, based on these data, 12 weeks of treatment with OMB/PTV-R + DAS may be considered in GT1a cirrhotic patients who are naïve or in whom prior relapse or partial response to previous PEG/RBV treatment has been confirmed. Therefore, the 24 week regimen should be considered for previous null responders with cirrhosis and GT1a infection.

Subpopulations:

CORAL-1 is an open-label, phase 2 trial evaluating OMB/PTV-R + DAS plus RBV for 24 weeks in 34 liver transplant patients with HCV GT1.[15] Patients were eligible if transplantation occurred at least 12 months before screening and if they had no evidence of fibrosis (Metavir ≤F2) and minimal hepatic impairment (Childs Pugh A). The median time since liver transplantation was 3.3 years and 71% had previously been treated with PEG/RBV before transplantation. SVR12 was achieved in 33 of the 34 patients (94%; 95% CI, 85 to 100%). All 33 patients continued to have an SVR at post-treatment week 24. This study has many limitations making it difficult to draw widespread conclusions on the efficacy and safety of OMB/PTV-R + DAS in liver transplant patients. The open-label, non-randomized study design with no comparator group adds significant risk of bias into the results. However, the effect size for the primary outcome remains large and it appears this may be a promising option. Further studies are warranted, particularly in patients with aggressive recurrence and/or decompensated hepatic function.

In an unpublished open-label trial, OMB/PRV-R + DAS plus RBV for 12 or 24 weeks was evaluated in 63 patients co-infected with HCV GT1 and HIV (TURQUOISE-I).[8] Overall, 24% of patients were black, 19% with compensated cirrhosis, and 67% were treatment naïve. SVR12 was achieved in 51 of the 56 patients (91%) with GT1a infection and 7 of the 7 patients with GT1b infection.[1] This trial remains unpublished and cannot be assessed for quality and risk of bias at this time.

Because ritonavir is also an HIV-1 protease inhibitor and can select for HIV protease inhibitor resistance-associated substitutions, HV/HIV co-infected patients treated with OMB/PRB-R + DAS should be on a suppressive antiretroviral drug regimen to reduce the risk of HIV-protease inhibitor drug resistance. Antiretroviral regimens need to be carefully evaluated for drug-drug interactions before co-administered with OMB/PRV-R + DAS treatment.

Clinical Safety:

Based on the two placebo-controlled trials (SAPPHIRE-1 AND –II), adverse events that occurred more often in those treated with OMB/PRB-R + DAS compared to placebo were fatigue, nausea, pruritus, other skin reactions, insomnia, and asthenia (Table 1).[1] Serious adverse events were rare and only occurred in 2% of patients. Less than 1% of subjects who discontinued treatment was due to adverse events. Without co-administration of RBV, the most common adverse reactions were nausea, pruritus and insomnia.

	Ombitasvir, paritaprevir/ritonavir plus dasabuvir (n=770) plus ribavirin	**Placebo (n=255)**
Fatigue	34%	26%
Nausea	33%	15%
Pruritus	18%	7%
Skin reactions	16%	9%
Insomnia	14%	8%
Asthenia	14%	7%

In PEARL III and IV, adverse events occurred more frequently in the groups receiving antiviral regimens that contained RBV than in the RBV-free groups, particularly pruritus, nausea, and insomnia. [13] Laboratory abnormalities, including decreased hemoglobin, occurred more frequently in those on RBV than those without (46.6% vs. 3.7%). In subjects treated with OMB/PRV-R + DAS without RBV, no subject developed a hemoglobin less than 10g/dl, while of subjects treated with ribavirin, less than 1% experienced a decrease to less than 8.0mg/dl during treatment. In TURQUOISE II, there was significantly more fatigue (46.5% vs. 32.7%), dyspnea (12.2% vs. 5.8%), upper respiratory tract infection (7.6% vs. 2.4%), back pain (7.6% vs. 1.9%), and memory impairment (7.0% vs. 2.4%) in the group receiving 24 weeks of therapy compared to the group receiving only 12 weeks.

The most common laboratory abnormality was a transient elevation in the total bilirubin level, due to the role of paritaprevir and ribavirin. Approximately 1% of subjects experienced post-baseline serum ALT levels greater than 5-times the upper limit of normal (ULN) after starting treatment. This occurred more frequently in female subjects who were using ethinyl estradiol-containing medications (9%), including oral contraceptives. These agents should be discontinued prior to starting therapy. This brings an additional concern, as RBV is a teratogen and female patients must use at least 2 effective means of contraception during treatment. Regular monitoring should be performed to evaluate elevations in ALT levels. Treatment should be considered for discontinuation if levels remain persistently greater than 10-times ULN, if an elevation is accompanied by signs and symptoms of liver inflammation, or significant increases in conjugated bilirubin, alkaline phosphatase, or INR are observed. Treatment is not recommended in patients with moderate to severe hepatic impairment until more data are available due to increased exposure of paritaprevir and dasabuvir in subjects with reduced hepatic function.[8]

Concomitant use with certain other drugs may result in significant drug interactions (Table 2 in Appendix 1), some of which may lead to loss of therapeutic effect of OMB/PRB-R + DAS.

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:

1) Hepatocellular Carcinoma
2) Mortality
3) Liver Transplant
4) Discontinuation Rates Due to Adverse Events

Primary Study Endpoint:

1) Sustained Virologic Response at week 12 after the end of treatment (SVR12)

Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Quality Rating/ Internal Validity Risk of Bias/ Applicability Concerns
SAPPHIRE-1[10] Phase III, DB, PC, RCT	1. OMB/PTV-R + DAS and RBV x 12 weeks 2. Placebo	Demographics: Treatment-naïve HCV genotype 1 patients without cirrhosis Mean age 49.4, 57.3% male; 90.5% white, 5.5% black Key Inclusion Criteria: HCV GT1, no cirrhosis, HCV RNA > 10,000 IU/ml, treatment-naive Key Exclusion Criteria: HBV, HIV, recent h/o of drug or alcohol abuse, uncontrolled diabetes, cirrhosis, CrCl < 60 ml/min, Platelets < 120,000	N= 1. 477 2. 159 ITT: 1.473 2.158	SVR12: 1. 455 subjects (96.2%; 95% CI, 94.5- 97.9%) This was noninferior and superior to the historical rate with telaprevir plus PEG/RBV GT1a: 95.5% GT1b: 98.0% Relapse: 1. 1.5% (95% CI, 0.4 to 2.6%)	N/A N/A	D/C due to Adverse event: 1. 3 (0.6%) 2. 1 (0.6%) RR (95% CI, x to x) p-value = NS Serious adverse events: 1. 10/473 (2.11%) 2. 0/158 (0%)	NS NS	**Quality Rating**: Fair-Good **Internal Validity (Risk of Bias)**: Selection: Randomization through an interactive response technology and computer generated sequence; significantly more males in treatment group compared to placebo (57.3% vs. 46.2%; p=0.02). Performance: Double-blinded Detection: Results also blinded Attrition: mITT analysis done; overall attrition low (<2%) **Applicability**: Patient: Significant inclusion and exclusion criteria decrease generalizability to hepatitis C population. In general, patients from were relatively healthy with few patients with advanced disease. Intervention: Appropriate intervention Comparator: No comparator group for efficacy; SVR was compared with an adjusted historical rate of 78% Outcomes: No long term clinical outcomes evaluated. SVR 24 data not included. Some evidence that SVR 24 is associated with improved clinical outcomes. Setting: Multicenter sites in North America, Europe, and Australia

SAPPHIRE-II[11] Phase III, DB, PC, RCT	1. OMB/PTV-R + DAS and RBV x 12 weeks 2. Placebo	Demographics: Treatment-experienced HCV GT1 patients without cirrhosis Mean age 51.7; 56.2% male; 90.6% white, 7.4% black Key Inclusion Criteria: Adherent to prior PEG/RBV therapy, HCV > 10,000 IU/ml Key Exclusion Criteria: H/o drug or alcohol abuse within 6 mo, HBV, HIV, uncontrolled diabetes, cirrhosis, CrCl < 60 ml/min, Platelets < 120,000	N= 1. 297 2. 98 ITT: 1.297 2.97	SVR12: 1. 286 subjects (96.3%; 95% CI 94.2-98.4) This was noninferior and superior to the historical rate with telaprevir plus PEG/RBV GT1a: 96.0% GT1b: 96.7% Relapse: 1. 7 2.4% (95% CI, 0.4 to 2.6%)	N/A N/A	D/C due to Adverse event: 1. 3 (1%) 2. 0 (0%) p-value = NS Serious adverse events: 1. 9/297 (3%) 2. 1/97 (1%)	NS NS	**Quality Rating**: Fair-Good **Internal Validity (Risk of Bias)**: Selection: Randomization through an interactive response technology and computer generated sequence. Groups similar at baseline. Performance: Double-blinded Detection: Results also blinded Attrition: mITT analysis done; overall attrition low (<2%) **Applicability**: Patient: Significant inclusion and exclusion criteria decrease generalizability to hepatitis C population. In general, patients from were relatively healthy with few patients with advanced disease. Intervention: Appropriate intervention Comparator: No comparator group for efficacy; SVR was compared with an adjusted historical rate of 65% Outcomes: No long term clinical outcomes evaluated. SVR 24 data not included. Some evidence that SVR 24 is associated with improved clinical outcomes. Setting: Multicenter sites in North America, Europe, and Australia
PEARL-II[12] Open-label, RCT	1. OMB/PTV-R + DAS plus RBV x 12 weeks 2. OMB/PTV-R + DAS x 12 weeks	Demographics: Treatment-experienced HDV GT1b patients without cirrhosis; mean age 54.2 Key Inclusion Criteria: HCV GT1b, no cirrhosis, previously failed treatment with PEG/RBV and adherent, HCV > 10,000 IU/ml	N 1. 92 2. 95 mITT: 1. 88 2. 91	SVR12: 1.85 (96.6%) 2. 91 (100%) Diff 3.4%; 95% CI -0.4-7.2 Both groups were noninferior and superior to the historical rate with telaprevir plus PEG/RBV	NS	D/C due to Adverse event: 1. 2 (2.3%) 2. 0 (0%) RR (95% CI, x to x) p-value = NS	NS	**Quality Rating**: Poor **Internal Validity (Risk of Bias)**: Selection: Randomization through an interactive response technology and computer generated randomization schedule; more males in group 2 (60% vs. 49%) and more patients with fibrosis score of 2 and 3 in group 2 Performance: Open-label Detection: Open-label Attrition: mITT analysis done; overall attrition low (<2%) **Applicability**: Patient: Significant inclusion and exclusion

		Key Exclusion Criteria: HBV, HIV, recent h/o of drug or alcohol abuse, uncontrolled diabetes, cirrhosis, CrCl < 60 ml/min, Platelets < 120,000, use of medications known to interact with ritonavir						criteria decrease generalizability to hepatitis C population Intervention: Appropriate intervention Comparator: Lack of placebo Outcomes: No long term clinical outcomes evaluated. SVR 24 data not included. Some evidence that SVR 24 is associated with improved clinical outcomes. Setting: Multicenter sites in North America, Europe, and Australia
PEARL-III[13]	1. OMB/PTV-R + DAS plus RBV x 12 weeks 2. OMB/PTV-R + DAS x 12 weeks	Demographics: Treatment-naïve HDV GT1b patients without cirrhosis; 42.5% male; 94% white; 10% F3 Key Inclusion Criteria: HCV GT1b, no cirrhosis, treatment-naive, HCV > 10,000 IU/ml Key Exclusion Criteria: HBV, HIV, recent h/o of drug or alcohol abuse, uncontrolled diabetes, cirrhosis, CrCl < 60 ml/min, Platelets < 120,000, use of medications known to interact with ritonavir	N 1. 210 2. 209 mITT: 1. 210 2. 209	SVR12: 1. 209 subjects (99.5%; 95% CI, 98.6 to 100%)) 2. 207 subjects (99%; 95% CI, 97.7-100%) Diff -0.5% (95% CI, -2.1 to 1.1%)* Both groups were noninferior and superior to the historical rate with telaprevir plus PEG/RBV *Group 2 (without RBV) was noninferior to group 1 (with RBV) Relapse: 1. 0 (0%) 2. 0 (0%)	NS NS	D/C due to Adverse event: 1. 0(0%) 2. 0 (0%) p-value = NS Serious adverse events: 1. 4 (1.9%) 2. 4 (1.9%)	NS NS	**Quality Rating**: Fair **Internal Validity (Risk of Bias)**: Selection: Randomization using computer generated schedule and interactive response technology; groups similar at baseline Performance: double-blinded to RBV only; RBV and matching placebos were identical in appearance Detection: Results also blinded Attrition: mITT analysis done; overall attrition low (<1%) **Applicability**: Patient: Significant inclusion and exclusion criteria decrease generalizability to hepatitis C population Intervention: Comparator: Lack of placebo Outcomes: No long term clinical outcomes evaluated. SVR 24 data not included. Some evidence that SVR 24 is associated with improved clinical outcomes. Setting: Multicenter sites in Austria, Belgium, Hungary, Israel, Italy, Poland, Portugal, Romania, Spain and the US
PEARL IV[13]	1. OMB/PTV-R + DAS plus RBV x 12 weeks 2. OMB/PTV-R +	Demographics: Treatment-naïve HDV GT1a patients without cirrhosis; 66% male, 17% F3,	N 1. 100 2. 205 mITT:	SVR12: 1. 97 subjects (97%; 95% CI, 93.7-100%) 2. 185 subjects (90.2%; 95% CI, 86.2-94.3%)	NS	D/C due to Adverse event: 1. 0 (0%) 2. 2 (1%) p-value = NS	NS	**Quality Rating**: Fair **Internal Validity (Risk of Bias)**: Selection: Randomization using computer generated schedule and interactive response

	DAS x 12 weeks	84% white Key Inclusion Criteria: HCV GT1a, no cirrhosis, treatment-naive, HCV > 10,000 IU/ml Key Exclusion Criteria: HBV, HIV, recent h/o of drug or alcohol abuse, uncontrolled diabetes, cirrhosis, CrCl < 60 ml/min, Platelets < 120,000, use of medications known to interact with ritonavir	1. 100 2. 205	Diff -6.8% (95% CI, -12 to -1.5%)* Both groups were noninferior and superior to the historical rate with telaprevir plus PEG/RBV *Group 2 did not meet noninferiority criterion compared with Group 1 Relapse: 1. 1 (1%) 2. 10 (5.2%)		Serious adverse events: 1. 3 (3%) 2. 1 (<1%)	NS	technology; groups similar at baseline Performance: double-blinded to RBV only; RBV and matching placebos were identical in appearance Detection: Results also blinded Attrition: mITT analysis done; overall attrition low (3.6%) and occurred all in placebo group. No discontinuations in RBV group. **Applicability**: Patient: Significant inclusion and exclusion criteria decrease generalizability to hepatitis C population Intervention: Comparator: Lack of placebo Outcomes: No long term clinical outcomes evaluated. SVR 24 data not included. Some evidence that SVR 24 is associated with improved clinical outcomes. Setting: Multicenter sites in Canada, US, and UK
TURQUOISE II[14] Open-label	1. OMB/PTV-R + DAS plus RBV x 12 weeks 2. OMB/PTV-R + DAS plus RBV x 24 weeks	Demographics: Treatment-naïve and –experienced with HCV GT1 with compensated cirrhosis 70% male; 94% white; mean age57 Key Inclusion Criteria: HCV GT1a, documented compensated cirrhosis (Child-Pugh score <7), HCV > 10,000 IU/ml Key Exclusion Criteria: HBV, HIV, recent h/o of drug or alcohol abuse, uncontrolled diabetes, cirrhosis, CrCl < 60 ml/min,	N 1. 209 2. 172 mITT: 1. 208 2. 172	SVR12: 1. 191 subjects (91.8%; 95% CI, 87.6 to 96.1%) 2. 165 subjects (95.9%; 95% CI, 92.6 to 99.3%) RR 0.93; 95% CI, 0.86 to 1.0; P=0.09 Both groups were noninferior and superior to the historical rate with telaprevir plus PEG/RBV in patients with cirrhosis Relapse: 1. 12 (5.9%) 2. 1 (0.6%) RR 9.9; 95% CI, 1.7 to 59	NS	D/C due to Adverse event: 1. 4 (1.9%) 2. 4 (2.3%) RR (95% CI, x to x) p-value = NS Serious adverse events: 1. 13 (6.2%) 2. 8 (4.7%)	NS NS	**Quality Rating**: Poor **Internal Validity (Risk of Bias)**: Selection: Unclear randomization method or how sequence generation was done; groups similar at baseline Performance: open-label Detection: Unclear Attrition: mITT analysis done; overall attrition low **Applicability**: Patient: Significant inclusion and exclusion criteria decrease generalizability to hepatitis C population. Only patients with Child-A cirrhosis were included (18.3% and 18.6% of patients with Child-Pugh score > 5 were included in the 12 week and 24 week arms, respectively). Eligibility criteria allowed for inclusion of patients with low platelets or albumin, however; median platelet count was only slightly lower than the normal limit and median albumin was within normal range. Results may differ in more advanced cirrhosis. Intervention:

		Platelets < 120,000, use of medications known to interact with ritonavir, prior therapy with DAAs, decompensated cirrhosis, hepatocellular carcinoma						Comparator: Lack of placebo Outcomes: No long term clinical outcomes evaluated. SVR 24 data not included. Some evidence that SVR 24 is associated with improved clinical outcomes. Setting: Multicenter sites in North American and Europe

Abbreviations [alphabetical order]: ARR = absolute risk reduction; CI = confidence interval; DB=double-blind; DAS = dasabuvir; GT = genotype; HBV = hepatitis B virus HCV = hepatitis C virus; ITT = intention to treat; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = nonsignificant; OMB=ombitasvir; PC=placebo-controlled; PEG = pegylated interferon; PP = per protocol; PTV-R=paritaprevir/ritonavir; RBV = ribavirin; RCT=randomized controlled trial; RR = relative risk; SVR12 = sustained virologic response 12 weeks after treatment is completed

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Appendix 1: Specific Drug Information[1]

CLINICAL PHARMACOLOGY

Viekira Pak includes ombitasvir, a hepatitis C virus NS5A inhibitor, paritaprevir, a hepatitis C virus NS3/4A protease inhibitor, ritonavir, a CYP3A inhibitor and dasabuvir, a hepatitis C virus non-nucleoside NS5B palm polymerase inhibitor.

PHARMACOLOGY AND PHARMACOKINETIC PROPERTIES:

Parameter	
Mechanism of Action	Combines 3 direct-acting antiviral agents with distinct mechanisms of action. Ritonavir is a potent CYP3A inhibitor that increases drug concentrations of paritaprevir and overall drug exposure.
Oral Bioavailability	The absolute bioavailability of ombitasvir, paritaprevir, and ritonavir was not evaluated.
Protein Binding	99.9% protein bound
Elimination	Ombitasvir: 90% in feces; Paritaprevir: 88% feces; Ritonavir: 11.3% urine, 86% feces; Dasabuvir: 94% feces
Half-Life	Ombitasvir: 21-25 hours; Paritaprevir: 5.5 hours; Ritonavir: 4 hours; Dasabuvir: 6 hours
Metabolism	Ombitasvir: amide hydrolysis followed by oxidative metabolism; Paritaprevir: CYP3A4; Ritonavir: CYP3A and CYP2D6; Dasabuvir: CYP2C8 and CYP3A

Sound-alike/Look-alike:
Ombitasvir, paritaprevir, and ritonavir + dasabuvir: NONE
Viekira Pak: Viagra, Viokace

DOSE & AVAILABILITY[1]

STRENGTH	ROUTE	DOSAGE/FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
Ombitasvir 12.5 mg, paritaprevir 75 mg, ritonavir 50 mg co—formulated tablets AND one dasabuvir 250 mg tablet	Oral	Two ombitasvir, paritaprevir, ritonavir 12.5/75/50 mg tablets once in the morning and one dasabuvir 250 mg tablet twice daily with a meal.	No dose adjustments recommended	Contraindicated in severe hepatic impairment.	Not established	No dose adjustment	• Used in combination with RBV in certain patient populations.

RECOMMENDED TREATMENT DURATION BY PATIENT POPULATION[1]:

Patient Population	Treatment*	Duration
Genotype 1a, without cirrhosis	VIEKIRA PAK + ribavirin	12 weeks
Genotype 1a, with cirrhosis	VIEKIRA PAK + ribavirin	24 weeks**
Genotype 1b, without cirrhosis	VIEKIRA PAK	12 weeks
Genotype 1b, with cirrhosis	VIEKIRA PAK + ribavirin	12 weeks
*Note: Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection. **VIEKIRA PAK administered with ribavirin for 12 weeks may be considered for some patients based on prior treatment history *[See Clinical Studies (14.3)]*.		

DRUG SAFETY[1]

Pregnancy/Lactation:

Pregnancy Category B: There are no adequate and well controlled trials in pregnant women. LDV/SOF should be used during pregnancy only if the potential benefit justified the potential risk to the fetus.

Lactation: Unknown if drug is present in human breast milk.

Serious (REMS, Black Box Warnings, Contraindications):

REMS: N/A

Black Box Warning: None

Contraindications: Contraindicated in patients with severe hepatic impairment and with drugs that are highly dependent on CYP3A for clearance (see table below)

Table 2. Drugs that are Contraindicated with VIEKIRA PAK

Drug Class	Drug(s) within Class that are Contraindicated	Clinical Comments
Alpha1-adrenoreceptor antagonist	Alfuzosin HCL	Potential for hypotension.
Anticonvulsants	Carbamazepine, phenytoin, phenobarbital	Ombitasvir, paritaprevir, ritonavir and dasabuvir exposures may decrease leading to a potential loss of therapeutic activity of VIEKIRA PAK.
Antihyperlipidemic agent	Gemfibrozil	Increase in dasabuvir exposures by 10-fold which may increase the risk of QT prolongation.
Antimycobacterial	Rifampin	Ombitasvir, paritaprevir, ritonavir and dasabuvir exposures may decrease leading to a potential loss of therapeutic activity of VIEKIRA PAK.
Ergot derivatives	Ergotamine, dihydroergotamine, ergonovine, methylergonovine	Acute ergot toxicity characterized by vasospasm and tissue ischemia has been associated with co-administration of ritonavir and ergonovine, ergotamine, dihydroergotamine, or methylergonovine.
Ethinyl estradiol-containing products	Ethinyl estradiol-containing medications such as combined oral contraceptives	Potential for ALT elevations *[see Warnings and Precautions (5.1)]*.
Herbal Product	St. John's Wort *(Hypericum perforatum)*	Ombitasvir, paritaprevir, ritonavir and dasabuvir exposures may decrease leading to a potential loss of therapeutic activity of VIEKIRA PAK.
HMG-CoA Reductase	Lovastatin,	Potential for myopathy including

Inhibitors	simvastatin	rhabdomyolysis.
Neuroleptics	Pimozide	Potential for cardiac arrhythmias.
Non-nucleoside reverse transcriptase inhibitor	Efavirenz	Co-administration of efavirenz based regimens with paritaprevir, ritonavir plus dasabuvir was poorly tolerated and resulted in liver enzyme elevations.
Phosphodiesterase-5 (PDE5) inhibitor	Sildenafil when dosed as REVATIO for the treatment of pulmonary arterial hypertension (PAH)	There is increased potential for sildenafil-associated adverse events such as visual disturbances, hypotension, priapism, and syncope.
Sedatives/hypnotics	Triazolam Orally administered midazolam	Triazolam and orally administered midazolam are extensively metabolized by CYP3A4. Coadministration of triazolam or orally administered midazolam with VIEKIRA PAK may cause large increases in the concentration of these benzodiazepines. The potential exists for serious and/or life threatening events such as prolonged or increased sedation or respiratory depression.

Table from Prescribing Information.[1]

Warnings and Precautions:

Increased Risk of ALT Elevation

Risk of HIV-1 Protease Inhibitor Drug Resistance in HCV/HIV-1 Co-infected Patients: Ritonavir is also an HIV-1 protease inhibitor and can select for HIV protease inhibitor resistance-associated substitutions. According to prescribing information, any HCV/HIV co-infected patients treated with ombitasvir, paritaprevir/ritonavir plus dasabuvir regimen should also be on a suppressive antiretroviral drug regimen to reduce the risk of HIV-1 protease inhibitor drug resistance. However, potential antiretroviral regimens that can be co-administered with the ombitasvir, paritaprevir/ritonavir plus dasabuvir regimen need to be carefully evaluated prior to initiation of the HCV regimen. Antiretroviral regimens evaluated in clinical studies which may be acceptable include tenofovir/emtricitabine in combination with either atazanavir 300mg (without ritonavir) once daily or raltegravir 400 mg twice daily. Antiretroviral regimens containing efavirenz, darunavir/ritonavir, lopinavir/ritonavir or rilpivirine are not recommended.

Appendix 2: Proposed PA Criteria

Hepatitis C Direct-Acting Antivirals

Goal(s):

- Approve cost effective treatments of chronic Hepatitis C, which are supported by the medical literature when there is available evidence.
- Treat the patient population in greatest need of treatment and who will benefit the most from therapy.
- Provide consistent patient evaluations across all hepatitis C treatments.

Length of Authorization:

- 8-12 weeks

Requires PA:

- All drug regimens in the Hepatitis C PDL Class

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is the request for treatment of Chronic Hepatitis C Virus?	**Yes:** Go to #3	**No:** Pass to RPh; deny for appropriateness.
3. What regimen is requested?	**Document and Go to #4.**	
4. Does the regimen contain a drug not yet reviewed by P&T?	**Yes:** Go to #5	**No:** Go to #6
5. Will the prescriber change to a preferred product already reviewed for efficacy and safety by the P&T Committee?	**Yes:** Inform Provider of covered alternatives in class	**No:** Pass to RPh; deny for appropriateness. Forward to DMAP for further review to determine appropriateness and coverage in light of most recent community standards and comorbidity.

Approval Criteria		
6. Is the medication being prescribed by or in consultation with a hepatologist or gastroenterologist with experience in Hepatitis C?	**Yes:** Go to #7.	**No:** Pass to RPh; deny for appropriateness. Forward to DMAP for further review to determine appropriateness of prescriber.
7. Does the patient have a biopsy or other non-invasive technology (Fibroscan), including serum tests (Fibrosure, Fibrotest) to indicate Advanced fibrosis (Metavir F3) or compensated cirrhosis (Metavir F4) OR radiologic, laboratory, or clinical evidence of cirrhosis without ongoing progressive decompensation (MELD score between 8 and 11), and expected survival from non-HCV associated morbidity should be greater than 5 years?	**Yes:** Go to #8.	**No:** Go to #9. **Note:** Patients with a MELD score >11 may be eligible for therapy, but only after review by the DMAP medical director. If patient has Metavir F0-F2, a treatment option remains pegylated interferon and ribavirin; refer to that specific PA Criteria
8. Does the patient have decompensated cirrhosis?	**Yes:** Pass to RPh; deny for appropriateness	No: Go to #11
9. Does the patient have one of the following extrahepatic manifestations of hepatitis C and who have formal documentation from a relevant specialist that their condition is HCV related, and expected survival from non-HCV associated morbidity should be greater than 5 years? a. Type 2 or 3 cryoglobulinemia with end-organ manifestations (vasculitis) b. Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis	**Yes:** Go to #11.	**No:** Go to 10.

Approval Criteria		
10. Does the patient have Hepatitis C Virus in the transplant setting, including the following scenarios: a) Patient is listed for a transplant and it is essential to prevent recurrent hepatitis C infection post-transplant b) Post-transplant patients with Stage 4 fibrosis c) Post-transplant patients with fibrosing cholestatic hepatitis due to HCV infection **And** expected survival from non-HCV associated morbidity should be greater than 5 years?	**Yes:** Go to #11.	**No:** Pass to RPh; deny for medical appropriateness. Note: Other scenarios not included can be brought to the Medical Director on a case by case basis.
11. Has the patient been abstinent from IV drug, illicit drugs and marijuana use, AND alcohol abuse for ≥ 6 months? AND If the patient has a history of alcohol abuse, has the patient been abstinent from alcohol use for ≥ 6 months?	**Yes:** Go to #12.	**No:** Pass to RPh; deny for appropriateness.
12. Does the patient have significant renal impairment (CrCl ≤30 mL/min) or end state renal disease (ESRD)?	**Yes:** Pass to RPh; deny for appropriateness.	**No:** Go to #13.
13. Does the patient have a baseline HCV RNA level?	**Yes:** Record value and go to #14	**No:** Pass to RPH. Request provider obtains baseline lab value.
14. What Hepatitis C genotype is the patient? Record Genotype:	Record Genotype and go to #15.	
15. Is the prescribed drug ledipasvir/sofosbuvir (Harvoni®) and is the regimen and duration appropriate for patient genotype based on the dosing and administration table below?	**Yes:** Approve for 8-12 weeks based on dosing and administration table.	**No:** Go to #16 If prescribed other DAA, encourage prescriber to use our preferred product
16. Is the prescribed drug sofosbuvir (Solvaldi®)?	**Yes:** Go to #17	**No:** Go to #18

Approval Criteria		
17. Does the patient have Genotype 2 hepatitis C infection?	**Yes:** Approve for 12 weeks based on dosing and administration table below	**No:** Go to #18 If prescribed other DAA, encourage prescriber to use our preferred product
18. Is the prescribed drug ombitasvir, paritaprevir, and ritonavir; dasabuvir (Viekira Pak®)?	**Yes:** Go to #19	**No:** Pass to RPh; deny for appropriateness. Encourage prescriber to use our preferred DAA.
19. Is the patient on any ethinyl estradiol containing products?	**Yes:** Pass to RPh; deny for appropriateness.	**No:** Go to #20
20. Does the patient have HIV coinfection?	**Yes:** Go to #21	**No:** Go to #22
21. Is the patient not receiving suppressive antiretroviral therapy (who may be at increased risk of HIV-1 protease inhibitor drug resistance) OR on therapy with significant antiretroviral drug-interactions (efavirenz, darunavir/ritonavir, lopinavir/ritonavir, rilpivirine).	**Yes:** Pass to RPh; deny for appropriateness.	**No:** Go to #22
22. Is the patient treatment naïve with or without cirrhosis or treatment experienced without cirrhosis?	**Yes:** Approve for 12 weeks based on appropriate dosing and administration from table below	**No:** Go to #23
23. Has the patient failed previous therapy with a direct acting antiviral?	**Yes:** Pass to RPh; deny for appropriateness. Use of Viekira has not been studied in this population.	**No:** Go to #24
24. If the patient failed previous therapy with peginterferon/ribavirin dual therapy, did the patient relapse or have a partial response?	**Yes:** Approve for 12 weeks based on dosing and administration table below	**No:** Go to #25

Approval Criteria		
25. Does the patient have cirrhosis and had a previous null response to dual therapy with peginterferon and ribavirin therapy or a post-liver transplant patient?	**Yes:** Approve for 24 weeks based on dosing and administration table below	**No:** Pass to RPh; deny for appropriateness. Encourage

Dosage and Administration:

Genotype 1			
Naïve	Without Cirrhosis and HCV RNA < 6 million IU/mL	LDV/SOF 1 tablet QDay	8 weeks
	Without Cirrhosis and HCV RNA ≥ 6 million IU/mL	LDV/SOF 1 tablet QDay	12 weeks
	Without Cirrhosis; Genotype 1b	Paritaprevir/R+Ombitasvir+Dasabuvir	12 weeks
	Without Cirrhosis; Genotype 1a	Paritaprevir/R+Ombitasvir+Dasabuvir + RBV	12 weeks
	With Cirrhosis	LDV/SOF 1 tablet QDay Paritaprevir/R+Ombitasvir+Dasabuvir + RBV	12 weeks 12 weeks
Experienced	Without Cirrhosis	LDV/SOF 1 tablet QDay Paritaprevir/R+Ombitasvir+Dasabuvir + RBV	12 weeks 12 weeks
	With Cirrhosis	LDV/SOF 1 tablet QDay + RBV Paritaprevir/R+Ombitasvir+Dasabuvir + RBV	12 weeks 12 weeks-24 weeks*
Genotype 2			
Naïve and Experienced	With or Without Cirrhosis	SOF 400 mg QDay + RBV	12 weeks**
Genotype 3			
Naïve or Experienced	With or Without Cirrhosis	LDV/SOF 1 tablet QDay + RBV	12 weeks
Genotype 4 and 6			
Naïve or Experienced	With or Without Cirrhosis	LDV/SOF 1 tablet QDay	12 weeks

*24 weeks of therapy with Paritaprevir/R+Ombitasvir+Dasabuvir + RBV should be reserved for treatment experienced, genotype 1a, null responders or post-liver transplant patients
**Previous nonresponders to PEG/RBV with cirrhosis may benefit by extension of therapy to 16 weeks
Abbreviations: LDV/SOF: Ledipasvir and sofosbuvir (Harvoni®); RBV: ribavirin; SOF: sofosbuvir (Sovaldi®)

P&T / DUR Action: 3/15(MH); 1/15(MH); 9/14(MH); 1/14(MH)
Revision(s): 1/15; 9/14; 7/14; 3/14
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Class Update with New Drug Evaluation: Long-Acting Opioids

Month/Year of Review: March 2015

Date of Last Review: March 2014

New Drugs:	Hydrocodone extended release (Hysingla ER®)	**Brand Name (Manufacturer):** Purdue Pharma
	Oxycodone/naloxone ER (Targiniq ER®)	Purdue Pharma
	Morphine/naltrexone ER (Embeda®)	Pfizer Pharmaceuticals

Current Status of PDL Class:

- Preferred Agents: FENTANYL ER TRANSDERMAL FILM (DURAGESIC®), MORPHINE SULFATE ER (MS CONTIN®)
- Non-preferred Agents: BUPRENORPHINE ER TRANSDERMAL FILM (BUTRANS®), HYDROMORPHONE ER (EXALGO®), LEVORPHANOL, METHADONE, MORPHINE SULFATE ER (AVINZA®, KADIAN®), MORPHINE SULFATE/NALTRESONE ER (EMBEDA®), OXYCODONE ER (OXYCONTIN®), OXYMORPHINE ER (OPANA ER®), TAPENTADOL ER (NUCYNTA®), TRAMDOL ER (ULTRAM ER®, CONZIP®), HYDROCODONE ER (ZOHYDRO ER®)

Research Questions:

- Is there any new comparative efficacy and effectiveness evidence of long-acting opioids (LAOs)?
- Is there any new comparative evidence of a meaningful difference in harms of LAOs?
- Is there any evidence that hydrocodone extended release (ER), oxycodone/naloxone ER, or morphine/naltrexone ER are more effective or safer than other LAOs?
- Are there subpopulations of patients for which one LAO medication or formulation is more effective or associated with fewer adverse effects?
- Is there any data supporting the use of any abuse deterrent product over non-abuse deterrent products?

Conclusions and Recommendations:

- There is low quality evidence of no clinically meaningful change in pain with hydrocodone ER compared to placebo, as rated on an 11-point pain-intensity numeric rating scale (difference in mean change from baseline -0.53; 95% CI -0.88 to -0.18, p-value 0.0016).[1,2]
- There is low quality evidence of no clinically meaningful change in pain with oxycodone/naloxone ER compared to placebo, as rated on an 11-point pain-intensity numeric rating scale (4.2 versus 3.7; 95% CI 0.1 to 0.8; p-value 0.006).[1,3]
- There is low quality evidence of no clinically meaningful change in pain with oxycodone/naloxone ER compared to placebo, as rated on the Brief Pain Inventory scale (-0.2 vs 0.3; p-value 0.0455).[1,3]
- There is insufficient evidence to establish differences in effectiveness of hydrocodone ER (Hysingla®) or oxycodone/naloxone ER (Targiniq®) versus other LAOs.

- There is insufficient evidence to establish differences in safety of hydrocodone ER (Hysingla®) or oxycodone/naloxone ER (Targiniq®) versus other LAOs.
- There is insufficient evidence to establish differences in safety of hydrocodone ER (Hysingla®) or oxycodone/naloxone ER (Targiniq®) versus other LAOs.
- There is insufficient comparative evidence in subpopulations to differentiate hydrocodone ER, oxycodone/naloxone ER, or morphine/naltrexone ER from other LAOs.
- There is insufficient evidence to determine whether an abuse-deterrent formulation of any LAO decreases the abuse or misuse of these drugs.
- Maintain hydrocodone ER, oxycodone/naloxone ER, and morphine/naltrexone ER as non-preferred and compare costs of other LAOs in executive session.

Previous Conclusions and Recommendations:

- There is insufficient comparative evidence to establish differences in effectiveness of hydrocodone ER (Zohydro® ER) versus the other LAOs.
- There is insufficient comparative evidence to establish differences in safety of hydrocodone ER versus other LAOs.
- There is insufficient comparative evidence in subpopulations to differentiate hydrocodone ER from the other LAOs.
- Maintain hydrocodone ER as non-preferred and evaluate comparative costs in executive session.

PA Criteria:
There is a maximum dose prior authorization (PA) required for doses greater than 120 morphine equivalent doses (MED) on all LAOs. Duplication of LAOs is not allowed except for cross-titration. Methadone carries an additional PA for initial doses above 20 mg per day when prescribed for pain. Methadone for addiction treatment is covered via professional claims (Appendix 1).

Background:

Chronic pain, often defined as pain lasting longer than 3 months or past the time of normal tissue healing, is common. Up to one-third of adults report chronic pain and it is a major cause of decreased quality of life and disability. Despite limited evidence showing long-term benefits, opioids are often used to treat chronic pain. [4] Using long acting opioids (LAOs) for cancer or end of life pain is widely accepted but treating chronic non-cancer pain with opioid therapy is more controversial.[4] Many pain guidelines advocate the use of LAO for chronic non-cancer pain despite limitations in evidence, escalating use, abuse and potential for life-threatening adverse effect. The Veterans Affairs/ Department of Defense Guidelines state that there is good evidence that LAO are effective for continuous pain.[5]

An Agency for Healthcare Research and Quality (AHRQ) class review on using LAOs for non-cancer pain cite that there is no clear evidence that a specific opioid has demonstrated superior efficacy or safety over another. [4] There is limited evidence on the safest and most effective way to initiate, titrate, transition and select LAO therapy. Guidelines recommend initiating opioids at a low dose and titrating the drug slowly, taking into account the specific pharmacokinetics of the drugs, in order to minimize adverse effects. No LAO has specifically been shown to be safer or more effective as initial therapy. Although opioids are viewed as having no maximum dose, guidelines recommend not exceeding 200 mg/day of oral morphine, or equivalent, in patients with chronic non-cancer pain.[6,7]

A variety of patient-reported pain scales are used to assess pain during clinical trials. Pain intensity is frequently measured on an 11-point pain intensity numerical rating scale (NRS), where 0 is no pain and 10 is worst possible pain. A change of -1.74 points and percent change score of -27.9% were best associated with a clinically important improvement using a NRS scale.[1] The Brief Pain Inventory (BPI) is a 17-item patient self-rating scale assessing demographic data, use of medications, and components of pain (including sensory and reactive components). A difference of 1 point on this scale is considered a minimally clinically important change.

Methods:
The DERP Scan[8] was used to identify any new comparative research that has emerged since the last P&T review.

New Systematic Reviews:
One new comparative effectiveness review from the AHRQ was identified.[4] This review required follow-up of greater than one year for most outcomes. Due to imprecision and methodological shortcomings, the strength of evidence was rated no higher than low with the exception of buccal or intranasal fentanyl for pain relief outcomes within 2 hours after dosing (strength of evidence: moderate). No study evaluated effects of long-term opioid therapy versus no therapy. Compared with non-use, long-term opioid therapy was associated with increased risk of abuse (one cohort study), overdose (one cohort study), fracture (two observational studies), myocardial infarction (two observational studies) and markers of sexual dysfunction (one cross-sectional study). One cohort study found methadone associated with lower risk of mortality than long-acting morphine in a Veterans Affairs population (HR 0.56, 95% Confidence Interval 0.51 to 0.62). Evidence was insufficient to evaluate benefits and harms of long-term opioid therapy in high-risk patients or in other subgroups.

New Guidelines:
American Pain Society: Methadone Safety (April 2014):

- Patient Assessment and Selection
    - Clinicians should perform an individualized medical and behavioral risk evaluation to assess the risks and benefits of methadone, given methadone's specific pharmacologic properties and adverse effect profile (strong recommendation, low-quality evidence)
- Patient Education and Counseling
    - Clinicians should educate and counsel patients prior to the first prescription of methadone about the indications for treatment and goals of therapy, availability of alternative therapies, and specific plans for monitoring therapy, adjusting doses, potential adverse effects, and methods for reducing the potential adverse effects and managing them (strong recommendation, low-quality evidence)
- Baseline Electrocardiograms (ECG)
    - Patients should have a baseline ECG prior to initiation of methadone in patients with risk factors for QTc interval prolongation, any prior ECG demonstrating a QTc >450 ms, or a history suggestive of prior ventricular arrhythmia (strong recommendation, low-quality evidence)
    - Consider obtaining and ECG prior to initiation of methadone in patients not known to be at higher risk of QTc prolongation (weak recommendation, low-quality evidence)
- Initiation of Methadone
    - Clinicians should initiate methadone at low doses individualized based on the indication for treatment and prior opioid exposure status, titrate doses slowly and monitor patients for sedation (strong recommendation, moderate-quality evidence)
    - Clinicians should consider those patients previously prescribed methadone, but who have not currently taken opioids for 1 to 2 weeks, opioid naïve for the purpose of methadone reinitiation (strong recommendation, low-quality evidence)
- Follow-up Electrocardiograms
    - For patients prescribed methadone, clinicians should preform follow-up ECGs based on baseline ECG findings, methadone dose changes, and other risk factors for QTc interval prolongation strong recommendation, low-quality evidence)
    - Methadone-treated adults with a QTc interval ≥500 ms should be switched to an alternative opioid or immediately reduce the methadone dose. (strong recommendation, low-quality evidence)

    - Clinicians should consider switching methadone-treated adults with a QTc interval ≥450 but <500 to an alternative opioid or reduce the methadone dose. Inpatients who cannot be switched, the clinician should discuss the risks of continued methadone with patients (strong recommendation, low-quality evidence)
    - In all cases where the QTc interval is >450 ms, the reversible causes of QTc prolongation should be corrected and the ECG should be repeated after the methadone dose has been decreased (strong recommendation, low-quality evidence)
- Monitoring and Managing Adverse Events
    - Patients receiving methadone should be monitored for common opioid adverse effects and toxicities and that adverse effects management be considered part of routine therapy (strong recommendation, moderate-quality evidence)
    - Face-to-face or phone assessments with patients should be conducted within 3 to 5 days after initiating methadone to assess adverse event. These assessments should be repeated within 3 to 5 days of each dose increase (strong recommendation, low-quality evidence)
- Urine Drug Testing
    - Clinicians should obtain urine drug screens prior to initiating methadone and at regular intervals in patients prescribed methadone for opioid addiction (strong recommendation, low-quality evidence)
    - Patients prescribed methadone for chronic pain who have risk factors for drug abuse should undergo urine drug testing prior to initiating methadone and at regular intervals thereafter; clinicians should consider urine drug testing in all patients regardless of assessed risk status (strong recommendation, low-quality evidence)
- Medication Interactions
    - Clinicians should use methadone with care in patients using concomitant medications with potentially additive side effects or pharmacokinetic or pharmacodynamics interactions with methadone (strong recommendation, low-quality evidence)
- Methadone Use In Pregnancy
    - Neonates born to mothers receiving methadone for neonatal abstinence syndrome should be monitored and treated when neonatal abstinence syndrome is present (strong recommendation, moderate-quality evidence)

New Safety Alerts:

Hydrocodone ER (Zohydro): Two black boxed warnings were issued. The first was a warning that prolonged use may result in neonatal opioid withdrawal syndrome and requires management according to protocols developed by neonatology experts. The second is that concomitant use of hydrocodone ER with all cytochrome P450 3A4 inhibitors or inducers as inhibitors may result in an increase in hydrocodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression, and discontinuation of a concomitantly used inducer may result in an increased hydrocodone plasma concentration. [8]

All extended release LAOs had a black box warning added to warn of[8]:

- The potential of addiction, abuse and misuse, which can lead to overdose and death.
- Serious, life-threatening, or fatal respiratory depression following dose increase or misuse of formulations (ie, chewing, crushing or dissolving a formulation which could cause rapid release and absorption).
- Neonatal opioid withdrawal syndrome with prolonged use of the drug during pregnancy.
- Interaction with alcohol which could cause increased plasma levels and a potentially fatal overdose of the opioid.

Risk Evaluation and Mitigation Strategies (REMS) are in place for LAOs to reduce these serious adverse events.

New Formulations or Indications:
None were identified.

Randomized Controlled Trials:

Eighty-two potentially relevant citations were evaluated from the literature search. Of these, there were 5 publications of 4 potentially relevant new drugs which are briefly described in the table below. [8] Full abstracts are included in **Appendix 2**.

Table 1: Description of Randomized Comparative Clinical Trials

Study	Comparison	Population	Primary Outcome	Results
Lowenstein, et al.[9]	Oxycodone ER vs oxycodone/naloxone ER	Adults with moderate-to-severe non-cancer pain	Improvement in Bowl Function Index (BFI) at 4 weeks	Oxycodone/naloxone ER showed a significant improvement in BFI compared with those in the oxycodone ER PR group (-14.9; 95% CI: -17.9, -11.9; p<0.0001)
Meissner, et al.[10] Nadstawek, et al.[11]	1. oxycodone ER/placebo 2. oxycodone/naloxone 10mg ER 3. oxycodone/naloxone 20mg ER 4. oxycodone/naloxone 40mg ER	Adults with severe pain	Improvement in Bowl Function Index (BFI) at 4 weeks	At week 4, the 20 mg and 40 mg naloxone groups showed a statistically significant improvement in the BFI compared to placebo (p<0.05). No analyses of change from baseline in BFI or other clinically relevant analyses were reported.
Perlman, et al.[12]	Methadone 1mg/1mL vs hydromorphone tab	Adults requiring dialysis with moderate-to severe pain	Mean percent change in plasma concentration of opioid after dialysis	More change in plasma concentration was seen with hydromorphone (55.1% vs 14.9%) showing a statistically significant difference of 40.2% (95% CI 17.14 to 63.14).
Vondrackova, et. al[13]	1. Oxycodone/naloxone ER 2. Oxycodone ER 3. placebo	Adults with moderate-to-severe low back pain	Time to recurrent pain events	Time was statistically significantly shorter in placebo group compare with oxycodone/naloxone ER (12 to 15 days, p-values between <0.001 and 0.003). There were no statistically significant differences between the oxycodone/naloxone ER and oxycodone ER groups.

NEW DRUG EVALUATIONS:

Hydrocodone ER (Hysingla®)[2,14]

Clinical Efficacy:

The efficacy of hydrocodone ER in moderate to severe chronic low back pain was assessed in one unpublished, 12 week, randomized, double-blind, placebo-controlled trial.[14] The study had an open-label run-in phase of up to 45 days designed to assess patients' qualification for randomization. During this period, patients started on either 20mg hydrocodone (opioid naïve patients) or a hydrocodone ER dose 25-50% of their incoming opioid daily dose.[2] Patients who demonstrated adequate analgesia (pain reduction of at least 2 points on an 11-point NRS to at least ≤4) and acceptable tolerability qualified for randomization in the 12-week double-blind period.[2] A total of 592 patients qualified for randomization.[2] Patients were randomized to the dose of hydrocodone they were stabilized on in the run-in period or placebo.[2] Patients randomized to placebo were tapered from their run-in dose of hydrocodone ER over the first 14 days of the study. Patients were allowed immediate release oxycodone 5-10 mg every 4-6 hours (up to 30 mg daily) as supplemental analgesic medication.[2] The primary efficacy endpoint was the "average pain over last 24 hours" scores during week 12 using an 11-point NRS, analyzed using Mixed-Effect Model Repeated Measure (MMRM).[2] The least squares mean difference in the primary endpoint compared to placebo was -0.53 (95% CI -0.88 to -0.18, p-value 0.0016).[2] This difference is not clinically significant.[1]

Clinical Safety:

The average daily dose of hydrocodone ER was 56.9mg in the double-blind period.[2] During the run-in period, the incidence of adverse events was 48%.[2] Adverse events that occurred at an incidence of ≥5% during the run-in period included nausea, vomiting, constipation, dizziness, headache and somnolence.[14] Confirmed or suspected diversion by patients overall during the 12-week study period was 4.3%.[14] Less than 1% of patients experienced adverse events associated with opioid withdrawal during the study period. [14]

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Pharmacology and Pharmacokinetic Properties[14]**:**

Parameter	
Mechanism of Action	Opioid receptor agonist, produces analgesia and sedation
Distribution and Protein Binding	Extensive tissue distribution 33%-37%
Excretion	Renal
Half-Life	8 hours
Metabolism	CYP3A4 (primary), CYP2D6, CYP2B6, CYP2C19, other; active metabolite (hydromorphone)

Look-alike / Sound-alike Error Risk Potential: none identified

Oxycodone /Naloxone ER (Targiniq ER®)[3]

Clinical Efficacy:
The efficacy of oxycodone/naloxone ER in patients with uncontrolled moderate to severe chronic low back pain was assessed in one unpublished, 12-week, randomized, double-blind, placebo-controlled trial. [3] A total of 1095 opioid-experienced patients were enrolled in a four week open-label, dose-titration period with oxycodone 5 mg for breakthrough pain. [3] The average age of patients was 54 years, and patients were predominantly Caucasian and female. [3] Only 55% of these patients achieved adequate analgesia and tolerability and were randomized to continue on active drug or switched to placebo. [3] Patients were allowed to continue taking immediate release oxycodone 5 mg for breakthrough pain, up to twice daily. [3] Overall attrition was high (33%) and more people in the placebo group discontinued due to lack of efficacy versus the treatment group (24% vs 10%). The primary efficacy outcome was average pain over the previous 24 hours at week 12 based on a MMRM analysis. [3] The difference between oxycodone/naloxone ER compared to placebo was statistically significant at 0.5 (4.2 for placebo versus 3.7 for oxycodone/naloxone; 95% CI 0.1 to 0.8; p-value 0.006) using an 11-point numerical pain rating scale. [3] This difference is not clinically significant.[1] No subgroup analyses (gender, age or race) resulted in any major or important differences within groups. [3]

Clinical Safety:
The most common adverse events reported by >5% of patients taking oxycodone/naloxone ER were nausea and vomiting. [3] There were no statistically significant differences in rates of serious adverse events or rates of overall adverse events [3]

Pharmacology and Pharmacokinetic Properties[15]**:**

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Parameter	
Mechanism of Action	Opioid receptor agonist, produces analgesia and sedation (oxycodone) Opioid antagonist that displaces narcotics at opioid receptor sites (naloxone)
Oral Bioavailability	60% to 87% (oxycodone); <3% (naloxone)
Distribution and Protein Binding	45% (oxycodone)
Excretion	Urine and feces (oxycodone and metabolites); urine (naloxone metabolites)
Half-Life	4-5 hours (oxycodone); 4-17 hours (naloxone)
Metabolism	CYP3A4, CYP2D6 (oxycodone); glucuronidation (naloxone)

Look-alike / Sound-alike Error Risk Potential: Targaniq may be confused with Talwin

Morphine ER/naltrexone (Embeda®)[3]

Clinical Efficacy:

The efficacy of morphine/naltrexone ER in patients with uncontrolled moderate to severe osteoarthritis pain was assessed in one unpublished, 12-week, randomized, double-blind, placebo-controlled trial.[16] A total of 547 patients were enrolled in an open-label, dose-titration period up to 6 weeks. [16] Only 344 (63%) of these patients achieved adequate analgesia and tolerability and were randomized to continue on active drug or switched to placebo. [16] The average age of patients was 54 years, and patients were predominantly Caucasian (72%) and female (58%). There was a slight imbalance in baseline characteristics between the groups: subjects in the treatment group were younger, had a higher BMI, were more likely to be female, and less likely to be Hispanic.[17] Overall attrition was high in the maintenance group (40%). More patients in the placebo group (43%) dropped out than the treatment group (36%); more patients withdrew for lack of efficacy in the placebo group (18.5%) than the treatment group (3.5%).[17] The primary efficacy outcome was average pain over the previous 7 days at week 12 using the Brief Pain Inventory (BPI) daily average pain scores, based on a last observation carried forward method. [16] The difference between oxycodone/naloxone ER compared to placebo was statistically significant at 0.5 (0.3 for placebo versus -0.2 for morphine/naloxone ER; p-value 0.0445) using the BPI scale. [3] This difference is not clinically significant.[1] No subgroup analyses (gender, age or race) were provided. [16]

Clinical Safety:

The most common adverse events reported by >5% of patients taking morphine/naltrexone ER were constipation and nausea.[17] There were no statistically significant differences in rates of serious adverse events or rates of overall adverse events. [17]

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Pharmacology and Pharmacokinetic Properties:

Parameter	
Mechanism of Action	Opioid receptor agonist, produces analgesia and sedation (morphine) Opioid antagonist that displaces narcotics at opioid receptor sites (naltrexone)
Oral Bioavailability	17-33% (morphine); 5-40%% (naltrexone)
Distribution and Protein Binding	20-35% (morphine); 21% (naltrexone)
Excretion	Urine and feces (morphine); urine (naloxone)
Half-Life	11-13 hours (morphine); 4 hours (naltrexone)
Metabolism	Hepatic via glucoronidation (morphine); urine (naltrexone)

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Appendix 1:

Opioid Analgesics – High Dose

Goal(s):

- Limit the use of high dose opioid therapy to above-the-line diagnoses that are supported by the medical literature
- Limit the use of non-preferred products
- Promote the safe use of opioids.
  - Opioids have been associated with an increasing proportion of deaths in Oregon and the US.
  - Opioid deaths in Oregon are often associated with concurrent use of other drugs (e.g. other opioids, benzodiazepines, skeletal muscle relaxants)
  - Opioid deaths in Oregon are often associated with patients with a history of drug abuse.
  - Buprenorphine, Fentanyl and Methadone carry FDA Black Box Warnings and have been associated with adverse cardiac effects associated with QTc prolongation and/or life-threatening hypoventilation.
    - This risk is increased with concurrent use of other drugs prolonging the QTc interval or other drugs affecting metabolism of methadone or fentanyl.
  - See Oregon DUR Board newsletter at:
    - http://pharmacy.oregonstate.edu/drug_policy/sites/default/files/pages/dur_board/newsletter/articles/volume11/durv11i2.pdf
    - http://pharmacy.oregonstate.edu/drug_policy/sites/default/files/pages/dur_board/newsletter/articles/volume5/durv5i5.pdf

Initiative:

Long and Short Acting Opioid quantity and dose limits: preferred agents, approved indications, and dose limits.

Length of Authorization:

Up to 6 months

Covered Alternatives:

A list of preferred opioids is available at www.orpdl.org

Requires a PA:

- All non-preferred opioids and preferred opioids exceeding the dose threshold in the table below, not to exceed a Morphine Equivalent Dose (MED) of 120 mg per day.
- Patient with terminal diagnosis, hospice, and metastatic neoplasm (ICD9 = 190xx – 199xx) are exempt from the PA requirements.

Approved Prior Authorizations may be subject to quantity limits.

Dosing Threshold adapted from Washington State Agency Medical Directors Interagency Guideline on Opioid Dosing for Chronic Non-cancer Pain 2010 (www.agencymeddirectors.wa.gov)

Opioid	Dose threshold	Recommended starting dose for opioid-naïve patients	Considerations
Buprenorphine Transdermal	20 mcg/hour (q 7 days)	5 mcg/hr patch q 7 days	May increase dose q72 hours patients up to a max of 20 mcg/hr q7 days. Doses >20 mcg/hr q7days increases risk of QTc prolongation.
Fentanyl Transdermal	50 mcg/hour (q72 hr)	Use only in opioid-tolerant patients who have been taking ≥ 60 mg MED daily for a week or longer	
Hydromorphone	30 mg per 24 hours	2 mg q4–6 hours	
Methadone	40 mg per 24 hours	2.5-5 mg BID – TID	Methadone is difficult to titrate due to its half-life variability. It may take a long time to reach a stable level in the body. Methadone dose should not be increased more frequently than every 7 days. Do not use as PRN or combine with other long-acting opioids.

Morphine	120 mg per 24 hours	Immediate-release: 10 mg q4 hours Sustained-release: 15 mg q12 hours	Adjust dose for renal impairment.
Oxycodone	80 mg per 24 hours	Immediate-release: 5 mg q4–6 hours Sustained Release: 10 mg q12 hours	See individual product labeling for maximum dosing of combination products. Avoid concurrent use of any OTC products containing acetaminophen (maximum dose = 4000 mg/day x <10 days or 2500 mg/day for 10 days or more)
Oxymorphone	40 mg per 24 hours	Immediate-release: 5–10 mg q4–6 hours Sustained Release: 10 mg q12 hours	**Use with extreme caution due to potential fatal interaction with alcohol or medications containing alcohol**.

Dosing Threshold for select short acting opioids		
Opioid	**Dose threshold**	**Considerations**
Codeine	800 mg/day	
Hydrocodone	120 mg/day	Dosing limits based on combinations (e.g. acetaminophen, ibuprofen) may lower the maximum daily dose

Common indications OHP does not cover:*	**ICD9 Codes**
Disorders of soft tissue (including Fibromyalgia)	*729.0-729.2,* *729.31-729.39,* *729.4-729.9,* *V53.02*
Acute and chronic disorders of spine without one of the following neurologic impairments: a. Reflex loss b. Dermatomal muscle weakness c. Dermatomal sensory loss d. EMG or NCV evidence of nerve root impingement e. Cauda equina syndrome f. Neurogenic bowel or bladder See Prioritized List of Health Services Guideline Notes 37 and 41	*721-724, except 723.3* *739, 839.2, 847*

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*Covered diagnoses are dependent on funding levels. A list of currently funded diagnoses can be found at www.oregon.gov/OHA/herc/pages/prioritizedlist.aspx

Approval Criteria		
1. What is the patient's diagnosis?	Record ICD9	
2. Is the request for methadone >100 mg?	Yes: Go to 3	No: Go to 5
3. Does the patient have any of the following QTc Risk Factors? • Family history of "long QTc syndrome", syncope, sudden death • Potassium depletion primary or secondary to drug use (i.e. diuretics) • Concurrent use of C34 inhibitors or QTc prolonging drugs (see table below) • Structural heart disease, arrhythmias, syncope	Yes: Go to 4	No: Go to 5

4. Is this new therapy (i.e. no previous prescription for the same drug last month)?	Yes: Pass to RPH; Deny, (Medical Appropriateness) Go over black box warning and offer alternatives (e.g. Fentanyl transdermal, morphine extended release).	No: Pass to RPH; approve for 30-60 days to allow time to taper or transition to alternative. Direct to DUR Newsletter for assistance. Refer to Rx "Lock-in" Program for evaluation and monitoring.
5. Is the patient being treated for any of the following: a. Oncology pain (ICD-9 338.3) b. Terminal diagnosis (<6 months) c. Hospice care	**Yes**: Go to #6	**No**: Go to #8
6. Is the requested medication a preferred agent?	**Yes:** Approve for up to 6 months	**No**: Go to #7
7. Will the prescriber consider a change to a preferred product?	**Yes**: Inform provider of covered alternatives in class.	**No**: Approve for up to 6 months
8. Will the prescriber consider a change to a preferred product not to exceed 120 mg MED?	**Yes**: Inform provider of covered alternatives in class.	**No:** Go to #9
9. Is the diagnosis covered by the OHP?	**Yes**: Go to #10	**No:** Pass to RPh, Deny (Not Covered by the OHP) May approve for 30-60 days to allow for tapering
10. Is this new therapy (i.e. no previous prescription for the same drug, same dose last month)?	**Yes**: Go to #11	**No**: Go To #12
11. Does the total daily opioid dose exceed 120 mg MED?	**Yes: Pass to RPh, Deny** (Medical Appropriateness) In general, the total dose of opioid should not exceed 120 mg MED Risks substantially increase at doses at or above 100 mg MED. Alternatives: Preferred NSAIDs or LAOs @ doses < 120 mg MED.	**No**: Go to #12
12. Has the patient had a recent urinary drug screen (within the past 90 days)?	**Yes**: Go to #13	No: Pass to RPH: Deny (Medical Appropriateness) Recommend Urine Drug Screen
13. Is the patient seeing a single prescribing practice & pharmacy for pain treatment (short and long acting opioids)?	**Yes**: Go To #14	**No:** <u>Approve 30-90 days;</u> Refer to Rx Lock-In program for evaluation. Further approvals pending RetroDUR / Medical Director review of case.

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14. Does the total daily opioid dose exceed 120 mg MED?	**Yes**: Go to #15	**No:** Go to #16
15. Can the prescriber provide documentation of sustained improvement in both function and pain AND is prescriber is aware of additional risk factors (e.g. concurrent benzodiazepines, skeletal muscle relaxants, other LAO or history of drug abuse)?	**Yes: Approve up to 6 months.** **Quantity Limits Apply, e.g.:** Avinza: 1 dose / day Butrans: 1 patch / week Embeda: 2 doses / day Exalgo: 1 dose / day Fentanyl: 1 patch / 72 hours Kadian: 2 doses / day Opana XR: 2 doses / day Oxycodone ER: 2 doses / day	**No:** Approve 30-90 days to allow for potential tapering of dose. Refer to Rx Lock-In program for evaluation. Further approvals pending RetroDUR / Medical Director review of case.
16. Is the patient concurrently on other long-acting opioids (e.g. fentanyl patches, methadone, or long-acting morphine, long-acting oxycodone, and long-acting oxymorphone)?	**Yes**: Go to #17	**No**: Approve for up to 6 months
17. Is the duplication due to tapering or switching products? The concurrent use of multiple long-acting opioids is not recommended unless tapering and switching products. Consider a higher daily dose of a single long-acting opioid combined with an immediate release product for breakthrough pain.	**Yes**: Approve for 30-90 days at which time duplication LAO therapy will no longer be approved.	**No: Deny** (Medical Appropriateness) **May approve for taper only.** Refer to Rx Lock-In program for evaluation. If necessary, inform prescriber of provider reconsideration process.

P&T or DUR Board Action: *3/15; 2/12; 11/11; 12/09; 9/09; 3/09; 12/08*
Revision(s): *6/12; 5/12; 1/12; 1/10*
Initiated: *7/09*

Appendix 2: Abstracts of Clinical Trials

Lowenstein O. Leyendecker P. Hopp M. Schutter U. Rogers PD. Uhl R. Bond S. Kremers W. Nichols T. Krain B. Reimer K (2009). Combined prolonged-release oxycodone and naloxone improves bowel function in patients receiving opioids for moderate-to-severe non-malignant chronic pain: a randomised controlled trial. Expert Opinion on Pharmacotherapy. 10(4):531-43, 2009.

BACKGROUND: This randomised, double-blind, double-dummy, parallel-group multicentre study assessed the impact of a total daily dose of 60-80 mg oral oxycodone prolonged-release (PR)/naloxone PR (OXN PR) as fixed-ratio combination for patients with opioid-induced constipation (OIC) having moderate-to-severe, non-malignant pain.

METHODS: During pre-randomisation patients receiving opioids for moderate-to-severe non-malignant pain were converted to oxycodone PR (OXY PR) and titrated to an effective analgesic dose. During randomisation 265 patients on a stable OXY PR dose (60-80 mg/day) and with OIC were included in the full analysis population to receive OXN PR or OXY PR alone. Primary outcome was improvement in symptoms of constipation as measured by the Bowel Function Index (BFI). Secondary/exploratory outcomes examined analgesic efficacy and other bowel function parameters.

RESULTS: After 4 weeks of treatment, patients receiving OXN PR showed a significant improvement in bowel function compared with those in the OXY PR group (-14.9; 95% CI: -17.9, -11.9; $p<0.0001$) as measured by BFI which was seen after only 1 week of treatment continuing to the end of the study. After 4 weeks of treatment, patients receiving OXN PR had a median number of 3.0 complete spontaneous bowel movements (CSBM) per week compared with only 1.0 for OXY PR alone. Laxative intake was lower in the OXN PR than the OXY PR group. Furthermore, improvements in bowel function were achieved without loss of analgesic efficacy; pain intensity scores were comparable between the groups and consistent for duration of the study. Most frequently reported adverse events were consistent with those reported for opioid analgesics; no new or unexpected adverse reactions attributable to OXN PR used in higher doses were observed.

CONCLUSION: This study shows that the fixed-ratio combination of OXN PR is superior to OXY PR alone in terms of bowel function, while providing effective equivalent analgesia. Unique Identifier: 19243306.

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Meissner W. Leyendecker P. Mueller-Lissner S. Nadstawek J. Hopp M. Ruckes C. Wirz S. Fleischer W. Reimer K (2009). A randomised controlled trial with prolonged-release oral oxycodone and naloxone to prevent and reverse opioid-induced constipation. European Journal of Pain. 13(1):56-64.

BACKGROUND: Opioid-induced constipation can have a major negative impact on patients' quality of life. This randomised, double-blinded study evaluated the analgesic efficacy of prolonged-release (PR) oral oxycodone when co-administered with PR oral naloxone, and its impact on opioid-induced constipation in patients with severe chronic pain. Another objective was to identify the optimal dose ratio of oxycodone and naloxone.

METHODS: A total of 202 patients with chronic pain (mainly non-cancer related, 2.5% of patients had cancer-related pain) under stable oral oxycodone therapy (40, 60 or 80 mg/day) were randomised to receive 10, 20, 40 mg/day naloxone or placebo. After a 4-week maintenance phase, patients received oxycodone only for 2 weeks. Pain intensity was evaluated using a numerical analogue scale and bowel function was assessed using the bowel function index.

RESULTS: No loss of analgesic efficacy with naloxone was observed. Mean pain intensity scores on randomisation were comparable for placebo, 10mg, 20mg and 40 mg naloxone dose, and remained unchanged during treatment. Bowel function improved with increasing naloxone dose. Naloxone 20mg and 40 mg significantly improved bowel function at the end of the maintenance phase compared with placebo ($p<0.05$). Overall, the combination was well tolerated, with no unexpected adverse events. There was a trend towards an increased incidence of diarrhoea with higher doses of naloxone. The 2:1 oxycodone/naloxone ratio was identified as the most suitable for further development.

CONCLUSION: Co-administration of PR oral naloxone and PR oral oxycodone is associated with a significant improvement in bowel function compared with PR oral oxycodone alone, with no reduction in the analgesic efficacy of oxycodone. Unique Identifier: 18762438.

Nadstawek J. Leyendecker P. Hopp M. Ruckes C. Wirz S. Fleischer W. Reimer K (2008). Patient assessment of a novel therapeutic approach for the treatment of severe, chronic pain. International Journal of Clinical Practice. 62(8):1159-67.

BACKGROUND AND OBJECTIVES: Opioid-induced constipation can have a major negative impact on patients' quality of life. This randomised clinical trial evaluated patient assessment of the efficacy and tolerability of oral prolonged-release (PR) oxycodone when co-administered with oral naloxone PR.
METHODS: Two hundred and two patients with chronic cancer- or non-cancer-related pain undergoing stable oxycodone PR therapy (40, 60 or 80 mg/day) were randomised to one of four intervention groups: 10, 20 or 40 mg/day naloxone PR or placebo. Following a 4-week maintenance phase, patients were followed-up for 2 weeks in which time they received oxycodone PR only. At the end of the maintenance phase, patients and investigators were asked to assess treatment efficacy and tolerability, as well as preference for the titration or maintenance phase.
RESULTS: Patient and investigator global assessment of efficacy and tolerability improved with increasing naloxone dose. Efficacy was ranked as 'good' or 'very good' by 50.0%, 67.4% and 72.5% of patients in the 10, 20 and 40 mg naloxone PR dose groups, respectively, compared with 43.5% of patients in the placebo group. Patient assessment of tolerability was similar between treatment groups and placebo, being ranked as 'good' or 'very good' by 83.3%, 79.1% and 82.5% of patients in the 10, 20 and 40 mg/day naloxone PR dose groups, respectively, compared with 71.7% of patients in the placebo group. The maintenance treatment phase was preferred by patients in the naloxone groups. A 2 : 1 dose ratio of oxycodone to naloxone was also assessed. Efficacy was ranked as 'good' or 'very good' by 70.4% of patients treated with the 2 : 1 dose ratio compared with 43.5% of patients receiving placebo. Tolerability of the 2 : 1 dose ratio was ranked as being 'good' or 'very good' by 81.5% of patients compared with 71.1% for the placebo group and patients preferred the maintenance phase.
CONCLUSIONS: The co-administration of oral naloxone PR with oxycodone PR improves patient assessment of analgesic opioid therapy for severe chronic pain, in terms of both efficacy and tolerability. Unique Identifier: 18705820.

Perlman R. Giladi H. Brecht K. Ware MA. Hebert TE. Joseph L. Shir Y (2013). Intradialytic clearance of opioids: methadone versus hydromorphone. Pain. 154(12):2794-800.
Opioids are commonly prescribed to patients with chronic pain associated with end-stage renal disease requiring hemodialysis. The stability of opioid analgesia during dialysis may vary among different opioids. No studies to date have corroborated this clinical observation by directly comparing plasma concentrations of different opioids during dialysis. We compared changes in peridialysis plasma concentrations of 2 pharmacokinetically distinct opioids, methadone and hydromorphone (HM). Fourteen dialysis patients with chronic pain received either methadone or HM for at least 2 weeks before beginning the study. Blood samples were obtained immediately before, during, and after hemodialysis in 2 separate dialysis sessions, 1 week apart, and were analyzed for opioid concentrations. Methadone plasma concentrations were more stable during hemodialysis compared to HM: the mean percent change of methadone plasma levels was 14.9% + 8.2% (+ SD) compared with 55.1% + 8.1% in the HM treatment group, a difference of 40.2% (95% confidence interval 17.14 to 63.14). The mean plasma clearance of methadone was 19.9 + 8.5 mL/min (+ SD) compared with 105.7 + 8.3 mL/min for HM, a difference of 85.7 mL/min (95% confidence interval 61.9 to 109.1). There were no differences between the 2 opioid groups in pain scores, side effect profile, and quality of life. Methadone therapy was not associated with an increased rate of adverse events. If confirmed by larger clinical studies, methadone could be considered as one of the opioids of choice in dialysis patients. Unique Identifier: 23973378.

Vondrackova D. Leyendecker P. Meissner W. Hopp M. Szombati I. Hermanns K. Ruckes C. Weber S. Grothe B. Fleischer W. Reimer K (2008). Analgesic efficacy and safety of oxycodone in combination with naloxone as prolonged release tablets in patients with moderate to severe chronic pain. Journal of Pain. 9(12):1144-54.
This randomized, double-blind, placebo- and active-controlled, parallel-group study was designed to demonstrate the superiority of oxycodone in combination with naloxone in a prolonged release (PR) formulation over placebo with respect to analgesic efficacy. The active control group was included for sensitivity and safety analyses, and furthermore to compare the analgesic efficacy and bowel function of oxycodone PR/naloxone PR with oxycodone PR alone. The analgesic efficacy was measured as the time from the initial dose of study medication to multiple pain events (i.e., inadequate analgesia) in patients with moderate to severe chronic low back pain. The full analysis population consisted of 463 patients. The times to recurrent pain events were significantly longer in the oxycodone PR/naloxone PR group compared with placebo (P < .0001-.0003); oxycodone PR/naloxone PR reduced the risk of pain events by 42% (P < .0001; full analysis population). The appearance of pain events was comparable for oxycodone PR/naloxone PR versus

oxycodone PR, confirming that the addition of naloxone PR to oxycodone PR in a combination tablet did not negatively affect analgesic efficacy of the opioid. Furthermore, oxycodone PR/naloxone PR offers benefits in terms of an improvement in bowel function. In a therapeutic area of great unmet need, therefore, the combination tablet of oxycodone PR/naloxone PR offers patients effective analgesia while improving opioid-induced bowel dysfunction. Taken together with the observation that the safety profile of oxycodone PR/naloxone PR is consistent with that expected from other opioid analgesics except opioid-induced constipation, these findings indicate that the addition of naloxone to oxycodone in a PR combination tablet offers improved tolerability. Oxycodone PR/naloxone PR is therefore a promising new treatment approach for the management of chronic pain.
PERSPECTIVE: This study evaluated the analgesic efficacy and safety of the combination of oxycodone PR/naloxone PR in chronic nonmalignant pain. Opioids are often reduced in dosage or even discontinued as a result of impaired bowel function, leading to insufficient pain treatment. Not only does oxycodone PR/naloxone PR demonstrate analgesic efficacy comparable with oxycodone PR, but it also improves opioid-induced bowel dysfunction, and may therefore improve the acceptability of long-term opioid treatment for chronic pain. Unique Identifier: 18708300.

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Class Review: Drugs for Constipation

Month/Year of Review: March 2015

Purpose for Class Review:
To identify appropriate utilization management strategies for drugs used to treat constipation, which is an unfunded condition on the Oregon Health Plan (OHP) Prioritized List of Health Services.

Research Questions:
- What is the current evidence and recommendations for the pharmacological management of constipation?
- Is there evidence of superior clinical efficacy or effectiveness for linaclotide, lubiprostone, alvimopan, methylnaltrexone or naloxegol over traditional laxatives used to manage constipation?
- Is there evidence of superior safety for linaclotide, lubiprostone, alvimopan, methylnaltrexone or naloxegol over traditional laxatives used to manage constipation?
- 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 constipation is more effective or associated with fewer adverse events?

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Conclusions:
- There is moderate quality evidence that osmotic and stimulant laxatives are associated with greater frequency of bowel movements and softer stool in chronic constipation relative to placebo; however, there is lower quality evidence for bulk-forming laxatives, saline laxatives and stool softeners. Comparative evidence suggests superior effectiveness with osmotic and stimulant laxatives relative to other laxatives. Significant heterogeneity, small numbers of study participants and short study durations limit most evidence associated with these traditional laxatives.
- There is moderate quality evidence that linaclotide and lubiprostone are efficacious in idiopathic constipation and irritable bowel syndrome with constipation compared to placebo. In addition, there is low quality evidence that lubiprostone is efficacious for opioid-induced constipation relative to placebo. There is insufficient evidence to determine if these drugs have superior efficacy relative to any traditional laxative.
- There is moderate quality evidence that peripheral-acting opioid antagonists methylnaltrexone and naloxegol are efficacious in opioid-induced constipation relative to placebo. Evidence for alvimopan in opioid-induced constipation is more limited. Background use of laxatives or other forms of bowel care were explicitly prohibited in Phase 3 studies of methylnaltrexone and naloxegol and therefore evidence is insufficient to determine if these two drugs have superior efficacy relative to any traditional laxative.
- There is insufficient quality evidence that linaclotide, lubiprostone, methylnaltrexone and naloxegol are safer for any duration relative to traditional laxative therapies. Potential risk for myocardial infarction limits use of alvimopan to hospital use only for post-operative ileus.

- There is insufficient evidence that one drug is more effective or associated with fewer adverse events in specific subgroups of patients based on demographics (age, racial or ethnic groups and gender), other medications (e.g., opioids), or most co-morbidities, with one exception: in patients with central neurological diseases and chronic constipation, low quality evidence suggests polyethylene glycol 3350 is effective at increasing frequency of bowel movements in patients with Parkinson's disease.

Recommendations:

- Implement prior authorization (PA) criteria for linaclotide, lubiprostone, alvimopan, methylnaltrexone and naloxegol to assure use for OHP-funded conditions. See proposed PA criteria in **appendix 5**.
- Establish a Laxatives drug class on the Preferred Drug List (PDL). Polyethylene glycol 3350, lactulose and senna products should be preferred products based on more robust evidence for effectiveness and safety around their use. At least one bulk-forming laxative and one saline laxative should also be preferred based on comparative pricing in the executive session.

Background:

Constipation is defined as unsatisfactory defecation characterized by infrequent tools, difficult stool passage, or both.[1] There are two types of constipation: primary (or idiopathic) constipation and secondary constipation. Primary constipation includes functional constipation, which includes chronic idiopathic constipation and constipation-predominant irritable bowel syndrome often associated with difficult or delayed evacuation, hard stools, abdominal bloating or discomfort.[1] Primary constipation also includes outlet obstruction (or defecatory disorder) associated with excessive straining and feeling of incomplete evacuation due to mechanical causes such as anal stricture, cancer, prolapse or pelvic floor dysfunction.[1] Secondary constipation can be due to diet, medications, lifestyle, pregnancy, advanced age or underlying medical conditions (e.g., diabetes mellitus, multiple sclerosis, Parkinson's disease or hypothyroidism, etc.).[1] Medications commonly associated with constipation are found in **appendix 1**.

The median prevalence of constipation from questionnaire-based epidemiologic studies is 16% in adults overall and 33.5% in adults aged older than 60 years.[2] Most studies suggest the prevalence of constipation is higher in females relative to males, in the nonwhite population relative to the white population, and in institutionalized persons relative to those in the community. Factors strongly associated with high risk for constipation include lower socioeconomic status and lower parental education rates, less physical activity, depression, physical and sexual abuse, stressful life events, and medications.[2] Medications most concerning for inducing constipation are opioids, in which there may be a prevalence of constipation in up to 50% of patients.[3] However, only about 20% of those suffering from constipation seek medical care; but because of its high prevalence, constipation consumes substantial health care resources.[2] In addition, women are more likely to use laxatives and seek health care for their constipation.[2]

Constipation is not currently covered under the Oregon Health Plan Prioritized List of Health Services.[4] Therefore, funding for drugs that treat constipation are dependent whether the constipation adversely affects, or is secondary to, the underlying medical condition covered by the Prioritized List.

Formulations, FDA indications and general dosing recommendations of currently available FDA-approved drugs are summarized in **table 1**. Pharmacologic treatments for constipation include several classes of medications with different mechanisms of action:

- Bulk-forming Laxatives: organic polymers that absorb water and increase stool mass, thereby making stool bulkier, softer and easier to pass.
- Stool Softeners: facilitate water interacting with the stool in order to soften the stool, make it more slippery and easier to pass.
- Osmotic Laxatives: poorly absorbed molecules that create an osmotic gradient within the intestinal lumen, drawing water into the lumen and making stool soft and loose.

- Stimulant laxatives: increase peristalsis in the colon and fluid and electrolyte secretion in the distal small bowel and colon.
- Secretagogues: increase chloride ion secretion into the intestinal lumen, thereby increasing intestinal fluid secretion and luminal water content and stool hydration. Linaclotide was already reviewed as an individual drug by the Oregon P&T committee in March 2013.[5]
- Peripheral-acting Opioid Antagonists: bind the mu-opioid receptors located within the GI tract, thereby decreasing the constipating effects of opioids.
    - Note: alvimopan is only approved to accelerate the time to GI recovery following partial bowel resection with primary anastomosis. A Risk Evaluation and Mitigation Strategy (REMS) is in place to limit its use to the labeled indication due to potential cardiac risk – in a hospital setting, for a maximum of 15 doses.[6]

Table 1. Currently Available Drugs for Constipation.[7,8]

DRUG NAME [TRADE NAME]	FDA INDICATION(S)	RX vs. OTC	FORMULATION/ ROUTE	GENERAL DOSING RECOMMENDATIONS (*refer to FDA labeling for specific dosing instructions*)
Laxatives, Bulk-forming				
Calcium Polycarbophil [FIBERCON, FIBER-LAX, etc.]	• Constipation or diarrhea	OTC	• 625 mg tab/PO	Adult, Child (≥12 y): 1250 mg up to QID Child (6-11 y): half adult dose
Methylcellulose [CITRUCEL, etc.]	• Adjunct in treatment of constipation	OTC	• Bulk pwdr/PO • 500 mg tab/PO	Powder: Adult, Child (≥12 y): 2 g (1 heaping TBSP) up to TID Child (6-11 y): half adult dose Tablet: Adult, Child (≥12 y): 2 tabs up to 6 times daily Child (6-11 y): half adult dose
Psyllium [METAMUCIL, etc.]	• Occasional constipation	OTC	• 520 mg cap/PO • Bulk pckt/PO • Bulk pwdr/PO	Supplement to general recommendations for TOTAL daily dietary fiber intake: Adults ≥51 y: males 30 g; females 21 g Adults 19-50 y: males 38 g; females 25 g Child 14-18 y: males 38 g; females 26 g Child 9-13 y: males 31 g; females 26 g Child 4-8 y: 25 g Child 1-3 y: 19 g
Laxatives, Lubricant				
Mineral Oil	• Temporary relief of occasional constipation • Temporary relief of occasional constipation • Relief of fecal impaction	OTC	• Oil/PO • Emulsion/PO • Enema/PR	Oil: Adult, Child (≥12 y): 15-45 mL/d in 1-4 divided doses Child (6-11 y): 5-15 mL/d in 1-4 divided doses Emulsion: Adult, Child (≥12 y): 30-90 mL/d in 1-4 divided doses Child (6-11 y): 10-30 mL/d in 1-4 divided doses. Enema: Adult, Child (≥12 y): 118 mL single dose Child (2-11 y): half adult dose

Laxatives, Saline				
Magnesium Citrate [CITROMA]	• Relief of occasional constipation	OTC	• 1.745 g/30 mL sol/PO	Adult, Child (≥12 y): 195-300 mL once or in divided doses Child (6-11 y): 90-210 mL once or in divided doses Child (2-6 y): 60-90 mL/day once or in divided doses
Magnesium Hydroxide [MILK OF MAGNESIA, PEDIA-LAX, etc.]	• Short-term relief of occasional constipation	OTC	• 400 mg/5 mL susp/PO • 800 mg/5 mL susp/PO • 400 mg tab/PO	Suspension: Adult, Child (≥12 y): 30-60 mL/d (400 mg/5 mL) or 15-30 mL/day (800 mg/5 mL) QHS or divided doses Child (6-11 y): half adult dose Child (2-5 t): 5-15 mL/d (400 mg/5 mL) QHS or divided doses Chewable Tablet: Child (6-11 y): 3-6 tab/d Child (2-5 y): 1-3 tab/d
Sodium Phosphates [FLEET ENEMA, etc.]	• Short-term relief of constipation	OTC	• Enema/PR • 2.4/0.9 g/5 mL sol/PO	Enema: Adult, Child (≥12 y): 4.5 oz enema as single dose Child (5-11 y): 2.25 oz enema as single dose Child (2-4 y): half of 2.25 oz enema as single dose Solution: Adult, Child (≥12 y): 15 mL up to TID Child (10-11 y): 15 mL/d Child (5-9 y): 7.5 mL/d
Laxatives, Surfactant (*stool softeners*)				
Docusate Calcium [KAO-TIN, etc.]	• Constipation associated with hard, dry stools • Prophylaxis for straining (valsalva) following myocardial infarction	OTC	240 mg cap/PO	Oral: Adult, Child (≥12 y): 50-500 mg/d in 1-4 divided doses Child (6-11 y): 40-150 mg/d in 1-4 divided doses Child (3-5 y): 20-60 mg/d in 1-4 divided doses Child (<3 y): 10-40 mg/d in 1-4 divided doses Rectal: Adult, Child (≥12 y): 50-100 mg as a single dose
Docusate Sodium [COLACE, etc.]		OTC	• 50-250 mg cap/PO • 100-283 mg/5 mL enema/PR • 50 mg/5 mL sol/PO • 60 mg/15 mL syrp/PO • 100 mg tab/PO	
Docusate Sodium/ Sennosides [PERI-COLACE, SENNA PLUS, etc.]	• Short-term relief of constipation	OTC	• 50/8.6 mg tab/PO	Adult, Child (≥12 y): 2 tabs daily to 4 tabs BID Child (6-11 y): half adult dose Child (2-5 y): ½ tab daily to 1 tab BID
Laxatives, Stimulant				
Bisacodyl [DULCOLAX, etc.]	• Constipation	OTC	• 10 mg supp/PR • 5 mg tab/PR	Oral: Adult: 5-15 mg as single dose Child (>6 y): 5-10 mg (0.3 mg/kg) as single dose Rectal: Adult Child (>2 y): 10 mg as single dose Child (<2 y): 5 mg as single dose

Senna [EX-LAX; SENNA-GEN, SENOKOT, etc.]	• Short-term relief of constipation	OTC	• Bulk leaves/PO • 8.8 mg/5 mL syrp/PO • 8.6-25 mg tab/PO • 15 mg chew tab/PO	Adult, Child (≥12 y): initial sennosides 15 mg once daily (max 70-100 mg/d divided BID) Child (6-11 y): initial sennosides 8.6 mg once daily (max 50 mg/d, divided BID) Child (2-5 y): initial sennosides 3.75 mg once daily (max 15 mg/d, divided BID)
Laxatives, Osmotic				
Glycerin	• Constipation	OTC	• 1-2 g supp/PR	Adult, Child (≥6 y): one adult suppository once Child (2-5 y): one pediatric suppository once
Lactulose (CONSTULOSE CHOLAC; GENERLAC, etc.)	• Constipation in adults	RX	• 10 g/15 mL sol/PO	Adult: 10-20 g daily (max 40 g/d) Child (off-label): 0.7-2 g/kg/d in divided doses (max 40 g/d)
Polyethylene Glycol 3350 [GLYCOLAX, MIRALAX, etc.]	• Occasional constipation in adults	OTC	• 17 g pckt/PO • Bulk pwdr/PO	Adult: 17 g daily Child (≥6 months) (off-label): 0.5-1.5 g/kg/d (max 17 g/d)
Sorbitol	• Constipation	OTC	• 70% sol/PO or PR	Oral: Adult, Child (>12 y): 30-150 mL single dose Child (2-11 y): 2 mL/kg single dose Enema: Adult, Child (>12 y): 120 mL once as a 25-30% solution Child (2-11 y): 30-60 mL once as a 25-30% solution
Opioid Antagonists, Peripherally-Acting				
Alvimopan (ENTEREG)	• Post-operative ileus	RX	• 12 mg cap/PO	Adult: 12 mg BID for post-operative ileus beginning at surgery for max 7 days or until discharged from hospital
Methylnaltrexone (RELISTOR)	• Opioid-induced constipation with chronic non-cancer pain • Opioid-induced constipation with advanced illness	RX	• 8 mg/0.4 mL or • 12 mg/0.6 mL sol/SC	Adult w/ non-cancer pain: 12 mg daily Adult w/ advance illness: Wt <38 kg: 0.15 mg/kg QOD PRN Wt 38 to <62 kg: 8 mg QOD PRN Wt 62 to 114 kg: 12 mg QOD PRN Wt >114 kg: 0.15 mg/kg QOD PRN
Naloxegol (MOVANTIK)	• Opioid-induced constipation	RX	• 12.5 mg tab/PO • 25 mg tab/PO	Adult: 25 mg daily; reduce to 12.5 mg daily if not tolerated or if CrCl <60 mL/min
Secretagogues				
Linaclotide (LINZESS)	• Chronic idiopathic constipation • Irritable bowel syndrome with constipation	RX	• 145 mcg cap/PO • 290 mcg cap/PO	Adult w/ idiopathic constipation: 145 mcg daily Adult w/ IBS constipation: 290 mcg daily
Lubiprostone (AMITIZA)	• Chronic idiopathic constipation • Opioid-induced constipation with chronic non-cancer pain • Irritable bowel syndrome with constipation in adult women	RX	• 8 mcg cap/PO • 24 mcg cap/PO	Adult w/ idiopathic constipation: 24 mcg BID Adult w/ opioid-induced constipation: 24 mcg BID Adult Females w/ IBS constipation: 8 mcg BID

Abbreviations: BID = twice daily; CrCl = creatinine clearance; FDA = Food and Drug Administration; IBS = irritable bowel syndrome; OTC = over-the-counter; PO = oral; PR = rectal; PRN = as needed; QHS = at bedtime; QID = four times daily; QOD = every other day; SC = subcutaneous; RX = prescription only; sol = solution; TBSP = tablespoon; TID = three times daily; wt = body weight; y = years

Highlights of prescribing information for the prescription products are available in **appendix 2**, which also highlights the Black Boxed Warnings in place for alvimopan and linaclotide.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to placebo or active controls were conducted. The Medline search strategy used for this literature scan is available in **appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Dynamed, 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 drugs, indications, and 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:
Evidence in systematic reviews is primarily limited to the traditional laxatives, linaclotide, lubiprostone, alvimopan and methylnaltrexone. However, methylnaltrexone data are primarily limited to palliative care. Efficacy and safety data for naloxegol and methylnaltrexone in patients with constipation due to opioids for chronic, non-malignant pain, of which both received FDA approval in 2014, are insufficiently available in systematic reviews at this time. Details of the trials reviewed by the FDA for approval are summarized in **appendix 3** along with comparative pharmacology and pharmacokinetic characteristics between these two drugs.

Included in this review are the high quality systematic reviewed performed in all forms of constipation since The Drug Effectiveness Review Project (DERP) at Oregon Health & Science University first performed their systematic review in 2007. The majority of systematic reviews assessed forms of constipation that are not covered under the OHP Prioritized List of Health Services: irritable bowel syndrome associated with constipation (IBS-C), opioid-induced constipation, and primary (idiopathic) constipation are unfunded conditions. However, these reviews are included for completeness in order to thoroughly assess how newer non-laxative drugs for different types of constipation compare to traditional laxatives.

Drug Effectiveness Review Project Review on Chronic Constipation (2007)[9]:
The Drug Effectiveness Review Project (DERP) performed a systematic review in 2007 on treatment of chronic constipation with or without IBS. All controlled, prospective studies were eligible for inclusion, regardless of sample size or study duration. The review identified seven head-to-head randomized controlled trials, sixteen placebo-controlled trials, one observational extension of an RCT, one meta-analysis, six observational studies and two pooled data analyses. The review rated the strength of evidence in a three-part hierarch (high, moderate or low) based on an approach devised by the GRADE working group that incorporates study design, study quality consistency of results and directness (availability of data). The review found that the general efficacy for most drugs was sparse, fraught with methodological issues or entirely missing.[9]

No controlled evidence was available for docusate calcium, docusate sodium or lactulose for the treatment of chronic constipation in adults. Three short-term trials (two weeks or less) demonstrated moderate strength evidence in adults for the efficacy of polyethylene glycol 3350 (PEG) but long-term data were missing. In one fair quality double-blind RCT, use of PEG 17 g daily was associated with greater treatment success, defined as more than 3 stools during a 7-day period, than placebo after 2 weeks (65.8% vs. 47.8%; p<0.001). The mean number of BMs was 4.5 for patients on PEG and 2.7 for patients on placebo (p<0.001). Two other trials showed similar efficacy of PEG. Evidence for psyllium 10.8 g daily in adults with chronic constipation was more limited and rated as low: two studies of mixed methodological quality indicated a beneficial effect for psyllium relative to placebo at improving bowel function (stool consistency, frequency of stools, ease of defecation, abdominal pain/discomfort or straining). At the time of the review, there were insufficient data on lubiprostone in adults to draw any conclusions on its efficacy. In general, lubiprostone had a statistically significant treatment benefit compared with placebo in trials of 3-4 weeks duration with consistently higher rates of spontaneous bowel movements within 24 hours. Head-to-head evidence was limited to 3 trials in adults comparing docusate sodium versus psyllium, lactulose versus PEG and PEG versus psyllium. Of these trials, one poor quality double-blind RCT showed no difference in efficacy between docusate sodium 200 mg daily and psyllium 10.2 g daily in terms of subjective outcomes; another poor quality open-label RCT reported greater straining (score for straining: 1.2 vs. 0.5; p=0.0001) and fewer weekly stools (0.9 vs. 1.3; p=0.005) with lactulose 10-30 g daily after 4 weeks of treatment compared to PEG 13-39 g daily. In one fair quality study, there was a statistically significantly greater improvement in weekly defecation rate in patients on PEG 25 g daily than on psyllium 7 g daily. No studies on the general efficacy for the treatment of chronic constipation in children were found. The evidence on the comparative efficacy of constipation in children was limited to one head-to-head trial of PEG 2.95 g daily and lactulose 6-12 g daily, in which both treatments significantly improved weekly bowel movements compared to baseline.[9]

The evidence for general tolerability and safety of these drugs is sparse and of poor quality. Few studies used objective scales and most combined patient-reported events with a clinical examination or laboratory values. Rarely were adverse events pre-specified or defined. Data suggests that lubiprostone has higher rates of nausea in adults than placebo, whereas there were not significant differences in adults between PEG or psyllium and placebo, although the information is limiting. In head-to-head evidence, PEG may be associated with less flatus and abdominal pain in adults than lactulose but no significant differences were noted between lactulose and psyllium or between PEG and psyllium. For children, PEG was well tolerated without any significant laboratory abnormalities and tended to be more tolerable than lactulose.[9] No serious adverse events were reported in any study.

There was not enough evidence in specific subgroups of patients based on demographics (age, racial or ethnic groups and gender), other medications or co-morbidities to determine if one drug is more effective or associated with fewer adverse events than another drug for chronic constipation.

Treatment for Chronic Idiopathic Constipation (2011)[10]:

A meta-analysis of RCTs at least one week in duration examining the effect of laxatives, which included all available laxatives broadly categorized as either osmotic or stimulant, or pharmacological therapies (lubiprostone or linaclotide) in adult patients with chronic idiopathic constipation (CIC) was performed. Studies that recruited patients with organic constipation, drug-induced constipation, or a highly select group (e.g., elderly institutionalized patients) were excluded from the review. The primary outcomes assessed were the efficacy of laxatives or pharmacological therapies compared with placebo in CIC, in terms of failure to respond to therapy or an effect on mean number of stools per week during treatment. A total of 11,077 citations were originally identified in the literature search, 49 of which appeared to be relevant; but upon further assessment, only 20 trials were eligible based on established inclusion and exclusion criteria for the review.[10]

Eight RCTs eligible for inclusion compared laxatives to placebo in 1442 CIC patients. Dichotomous data were reported by seven RCTs evaluating laxatives: 351 (40.1%) of 876 patients assigned to laxatives failed to respond to therapy, compared to 392 (73.3%) of 535 allocated to placebo (relative risk (RR) of failure to respond = 0.52; 95% confidence interval (CI), 0.46 to 0.60), with borderline heterogeneity between studies (I^2=42%; p=0.11). The number needed to treat (NNT) to prevent 1 patient failing to respond to therapy was 3. Sensitivity analyses did not affect the outcomes, with a NNT ranging from 3-5. There was no statistically significant funnel plot asymmetry suggesting no evidence of publication bias or other small study effects.[10] Details on these results are summarized in **table 2**.

Continuous data were reported in six laxative studies. Mean number of stools per week was significantly higher with laxatives compared to placebo (weighted mean difference (WMD) in number of stools per week = 2.55; 95% CI, 1.53 to 3.57) with statistically significant heterogeneity between studies (I^2=100%; p<0.001) but no evidence of funnel plot asymmetry. The beneficial effect was seen with both osmotic and stimulant laxatives.[10]

The RR of experiencing any adverse event with laxatives was 1.94 (95% CI, 1.52 to 2.47; NNH=3). No significant differences in rate of abdominal pain were observed, but diarrhea was observed significantly more frequently with laxatives (RR=13.75; 95% CI, 2.82 to 67.14; NNH=3).[10]

Three RCTs eligible for inclusion compared lubiprostone to placebo in 610 CIC patients. Only one trial was at low risk of bias. There were 151 (45.1%) of 335 patients receiving lubiprostone who failed to respond to therapy compared to 184 (66.9%) of 275 placebo patients (RR of failure to respond to therapy = 0.67; 95% CI, 0.56 to 0.80), with no significant heterogeneity between studies (I^2=30%; p=0.24). The NNT for lubiprostone was 4. Total numbers of adverse events were significantly higher with lubiprostone (RR=1.79; 95% CI 1.21 to 2.65; NNH=4), with diarrhea and nausea occurring most frequently.[10]

The 3 RCTs comparing linaclotide to placebo involved 1582 patients with CIC. All three trials were at low risk of bias. There were 860 (79.0%) of 1089 patients receiving linaclotide who failed to respond to therapy compared to 468 (94.9%) of 493 placebo patients (RR of failure to respond to therapy = 0.84; 95% CI 0.80 to 0.87), with no significant heterogeneity between studies (I^2=32%; p=0.23). The NNT for linaclotide was 6. Analyses according to dose of linaclotide used demonstrated similar efficacy for 133 mcg and 266 mcg daily (RR=0.85 and 0.84, respectively). Total numbers of adverse events with linaclotide were similar to placebo.[10]

Table 2. Failure to Respond to Therapy in Chronic Idiopathic Constipation Relative to Placebo in Randomized Controlled Trials.[10]

Therapy	Relative Risk (95% Confidence Interval) to Placebo	Number Needed to Treat
Osmotic Laxatives	0.50 (0.39 to 0.63)	3
Stimulant Laxatives	0.54 (0.42 to 0.69)	3
Lubiprostone	0.67 (0.56 to 0.80)	4
Linaclotide	0.84 (0.80 to 0.87)	6

Cochrane Review on Treatment of Constipation with Laxatives or Methylnaltrexone in Palliative Care (2011)[11]:

Palliative care patients commonly experience constipation as a result of medications, particularly opioids, for pain control, as well as disease, dietary and mobility factors. The objective of this Cochrane review was to determine the effectiveness of laxatives or methylnaltrexone for the management of constipation in palliative care patients.[11] All laxatives administered for the management of constipation in palliative care for cancer and other long-term progressive medical conditions were eligible for inclusion. Only seven RCTs involving 616 patients met criteria for inclusion, which included studies that either compared the effectiveness of two different laxatives, compared methylnaltrexone with a placebo, or different doses of methylnaltrexone. None of the studies compared the effectiveness of methylnaltrexone with a laxative and none of the trials compared a laxative to placebo. None of the studies reported methods to conceal

random allocation, and blinding was not possible in the laxative trials owing to differences in the physical characteristics of the drugs. No differences in effectiveness were found between lactulose and senna, lactulose with senna compared to magnesium hydroxide and liquid paraffin (mineral oil), or between misrakasneham (a traditional Indian herbal product) and senna. Another study found a statistically significant increase in stool frequency with those who took lactulose and senna compared to those who took co-danthramer (stimulant laxative), though there were no differences between these two groups in patient's assessment of bowel function. In general, laxatives were well tolerated in these studies with only a few patients reporting adverse effects; primarily nausea, vomiting, diarrhea and abdominal pain. Most evidence identified in this review was on the effect of methylnaltrexone, based on evidence from two studies involving 287 patients. Methylnaltrexone was statistically significantly more effective at inducing a bowel movement than placebo; and that this response was generally rapid. It is important to note that most patients received background laxative therapy and were constipated at baseline. It is unclear, however, the frequency at which patients took conventional laxative therapy in these trials. Overall, methylnaltrexone was well tolerated though flatulence and dizziness were more common with methylnaltrexone therapy than placebo. In all studies identified in this review a number of patients remained constipated and were given rescue laxatives. None of the studies explored differences in follow-up characteristics, such as disease progression or drug use, between responders and non-responders. Conclusions on the optimal laxative management of constipation in palliative care patients cannot be made from this review as research remains limited. Specifically, there have been no RCTs on any laxative that has evaluated response rate, patient tolerability and acceptability. From the available comparative data however, the review concluded that lactulose and senna had similar effectiveness in this population and methylnaltrexone demonstrated short-term efficacy relative to placebo in patients where conventional laxative therapy was sub-optimal.[11]

Cochrane Review on Management of Fecal Incontinence and Constipation in Adults with Central Neurological Diseases (2014)[12]:
People with central neurological disease or injury have a much higher risk of both fecal incontinence and constipation than the general population. There is a fine balance in managing these two symptoms, with any management intended to ameliorate one risking precipitating the other. According to the review, current pharmacological bowel management is largely empirical with research in this population limited to two laxatives: psyllium, the bulk-forming laxative, and PEG, an osmotic laxative. The evidence for these two agents come from two small trials in patients with Parkinson's disease that had a statistically significant improvement in the number of weekly BMs when 8 weeks of psyllium 5.1 g daily or PEG 7.3 to 21.9 g daily were compared to placebo (see **table 3**). In the psyllium trial, run-in periods and washout periods were appropriate, but there were only 3 patients in the psyllium group and 4 patients in the placebo group. The PEG trial was also 8 weeks in duration and was relatively larger than the psyllium trial with 57 participants. Adverse events were not reported in either trial.[12]

Table 3. Mean Difference in Weekly Bowel Movements Relative to Placebo in Patients with Parkinson's Disease.

Drug Studied	Mean Difference in Weekly Bowel Movements Relative to Placebo	Relative Risk of Failure to Respond to Therapy
Psyllium	2.2 (95% CI, 1.4 to 3.3)	n/a
Polyethylene glycol	2.9 (95% CI, 1.5 to 4.3)	0.29 (95% CI, 0.11 to 0.72)

Cochrane Review on Osmotic and Stimulant Laxatives for the Management of Childhood Constipation (2013)[13]:
Childhood constipation is a very common problem that is commonly treated with osmotic and stimulant laxatives despite a long-standing paucity of high quality evidence to support the practice. Randomized controlled trials comparing an osmotic or stimulant laxative to either placebo or another intervention with a primary outcome of frequency of BMs in patients aged 0 to 18 years were eligible for inclusion. Eighteen RCTs (1643 patients) were included in the review, nine of which were at high risk of bias due to lack of blinding, incomplete outcome data and selective reporting. In a meta-analysis of two studies (n=101) comparing PEG with placebo, there was a significantly increased number of weekly BMs with PEG but at the cost of more flatulence, abdominal pain, nausea, diarrhea and headache. In a meta-analysis of four short-term studies (n=338), PEG also significantly increased number of weekly BMs compared to lactulose without any

serious adverse events. Patients who received PEG were also significantly less likely to require additional laxative therapy versus lactulose (18% vs. 30%, respectively; odds ratio 0.49; 95% CI 0.27 to 0.89). In a meta-analysis of three studies (n=211), PEG also statistically significantly increased number of weekly BMs compared to milk of magnesia but the clinical significance of this difference is questionable. In a meta-analysis of two studies (n=287) comparing mineral oil with lactulose, mineral oil significantly increased number of weekly BMs relative to lactulose without any serious adverse events, though there were cases of abdominal pain, distention and diarrhea. The results of these studies are illustrated in **table 4**. Weekly BMs were comparable between monotherapy with PEG relative to enemas (1 study, 90 patients, MD 1.00; 95% CI, -1.58 to 3.58), dietary fiber with lactulose (1 study, 125 patients; p=0.481), senna with lactulose (1 study, 21 patients; p>0.05), lactitol with lactulose (1 study, 51 patients, MD -0.80; 95% CI, -2.63 to 1.03), and PEG with mineral oil (1 study, 158 patients, MD 0.70; 95% CI, -0.38 to 1.78). The review suggests that PEG may be superior to placebo, lactulose and milk of magnesia for childhood constipation and relatively comparable to enemas and combination therapy including lactulose. However, short follow-up, sparse data, heterogeneity between the studies, and high risk of bias limit the evidence to low or very low quality and results should be interpreted cautiously.[13]

Table 4. Mean Difference in Weekly Bowel Movements in Children Treated with Different Laxatives.

Drugs Studied	Mean Difference in Weekly Bowel Movements
Polyethylene glycol vs. Placebo	2.61 (95% CI, 1.15 to 4.08)
Polyethylene glycol vs. Lactulose	0.95 (95% CI, 0.46 to 1.44)
Polyethylene glycol vs. Milk of Magnesia	0.69 (95% CI, 0.48 to 0.89)
Mineral oil vs. Lactulose	4.94 (95% CI, 4.28 to 5.61)

An older meta-analysis with similar inclusion criteria also found PEG achieved more treatment success (RR 1.47; 95% CI, 1.23 to 1.76) compared to other laxatives. However, significant heterogeneity between PEG trials existed, and data had to be pooled comparing PEG with any laxative rather than a specific laxative. Lactulose was less than or equally effective in increasing frequency of BMs compared to other laxatives investigated. There was no difference in effect on frequency of BM between fiber and placebo in children (MD 0.35; 95% CI, -0.04 to 0.74). However, due to the insufficiency of the data, particularly around conflicting results found with the use of PEG, the authors were not able to provide recommendations to support one laxative over the other for childhood constipation.[14]

A systematic review specifically assessing PEG in children with constipation also showed similar results, but the significant heterogeneity of the studies prohibited the authors from performing a meta-analysis.[15]

Cochrane Review of Lactulose versus Polyethylene Glycol for Chronic Constipation in Adults and Children (2010)[16]:
Lactulose and PEG are both commonly used osmotic laxatives that shown to be safe and effective for the treatment of chronic constipation in children and adults. This meta-analysis identified all relevant data from ten RCTs in children and adults (n=868) to determine whether lactulose or PEG was more effective at treatment chronic constipation and fecal impaction. Four of the studies included adults and five trials reported weekly BMs. Together, these trials demonstrated statistically significant superiority with PEG compared to lactulose in mean difference of weekly BMs. In children, the difference was even more pronounced. In adults, the difference was smaller but still statistically significant though the clinical significance of this difference may not be important. Results are provided in **table 5**. In studies reporting the Bristol Stool Scale, use of PEG resulted in a higher Bristol Stool Score (softer stool) relative to lactulose. Three trials reported relief of abdominal pain: two of the trials showed use of PEG was associated with less abdominal pain relative to lactulose and one trial showed them to be relative equal in this outcome. Together, the odds of developing abdominal pain remained significantly greater with lactulose, which was more pronounced in children relative to adults (see **table 6** for details). All three trials reporting on the use of additional laxatives or other drugs showed that lactulose was associated

with significantly greater use of other drugs to manage constipation (OR 4.00; 95% CI, 2.01 to 7.95). The odds of needing additional therapy were greater in children than adults (OR 5.69, 95% CI, 2.06 to 15.68 vs. OR 2.79, 95% CI, 1.07 to 7.27, respectively). Limitations include significant heterogeneity between trials (I^2 = 77%).[16]

Table 5. Difference in Weekly Bowel Movements Between Polyethylene Glycol and Lactulose in Children and Adults.

Drugs Studied	Mean Difference in Weekly Bowel Movements
Polyethylene Glycol vs. Lactulose (all)	0.65 (95% CI, 0.15 to 1.15)
Polyethylene Glycol vs. Lactulose (adults only)	0.28 (95% CI, 0.10 to 0.45)
Polyethylene Glycol vs. Lactulose (children only)	1.57 (95% CI, 0.36 to 2.77)

Table 6. Odds of Developing Abdominal Pain with Lactulose Compared to Polyethylene Glycol in Children and Adults.

Drugs Studied	Odds of Developing Abdominal Pain
Lactulose vs. Polyethylene Glycol (all)	2.09 (95% CI, 1.26 to 3.44)
Lactulose vs. Polyethylene Glycol (adults only)	0.86 (95% CI, 0.25 to 2.90)
Lactulose vs. Polyethylene Glycol (children only)	2.52 (95% CI, 1.45 to 4.40)

In a separate meta-analysis with similar inclusion criteria but restricted to adult populations, use of PEG resulted in a highly significant increase in weekly BMs compared to placebo (all studies: MD 1.98, p=0.0003; high quality studies: MD 2.34, p=0.001) and when compared to lactulose (all studies: MD 1.0, p=0.0017; high quality studies: MD 1.65, p=0.021).[17]

11

Cochrane Review of Mu-opioid Antagonists for Opioid-induced Bowel Dysfunction (2008)[18]:

Opioid-induced bowel dysfunction occurs both acutely and chronically, in multiple disease states, resulting in increased morbidity and reduced quality of life due to increased symptoms of constipation, incomplete evacuation, bloating and increased gastric reflux. This review and meta-analysis identified all relevant data from twenty-three RCTs (n=2871) assessing the efficacy of mu-opioid antagonists in opioid-induced bowel dysfunction. However, only four studies (n=147) investigated an opioid antagonist for treatment of OIC in patients with cancer pain, chronic non-cancer pain and methadone maintenance. Opioid antagonists included in the review for treatment of OIC were alvimopan (1 study), methylnaltrexone (1 study) and naloxone (2 studies). Of these, alvimopan and methylnaltrexone are peripheral-acting opioid antagonists and therefore specifically block receptors in the bowel without crossing the blood-brain barrier and blocking opioid receptors in the brain and reversing reduction in pain. Assessment of constipation varied between the studies and included composite scales, proportion of patients with a BM within a specified time period, small bowel transit time, stool frequency, and overall patient satisfaction, which led to significant heterogeneity (I^2 = 98%). In the alvimopan study, 54% of patients receiving alvimopan had a BM within 8 hours of administration versus 30% of those receiving placebo (NNT 5). In the methylnaltrexone study, 100% of patients receiving methylnaltrexone had an immediate BM versus none in the placebo group (NNT 1). When both studies were combined using a fixed-effects model, the use of an opioid antagonist produces a NNT of 3. However, when a random-effects model was employed to adjust for between study heterogeneity, the combined effect observed in the two studies was no longer statistically significant. In the studies assessing weekly BMs, combined data showed an opioid antagonist induced 1.4 more weekly BMs than placebo (95% CI, 0.2 to 2.5). In the 3 studies assessing patient satisfaction, each study showed significant improvement in patient satisfaction when receiving an opioid antagonist compared to placebo, with methylnaltrexone appearing to have the greatest improvement (100% of patients satisfied vs. 22% of patient receiving placebo). Combining the data with a

fixed-effect model showed 75% of patients receiving an opioid antagonist were satisfied versus 44% of those receiving placebo (NNT 4). The small sample sizes of these trials and significant heterogeneity between them may limit the interpretation of these results.[18]

Efficacy and Safety of Polyethylene Glycol compared to Lactulose, Docusate Sodium and Senna in Opioid-induced Constipation (2013)[19]:
This systematic review sought to find whether docusate sodium, sennosides and lactulose use in the prevention and management of OIC have equal efficacy and adverse effect profiles compared to PEG in adults receiving opioid treatment for a variety of outcomes. Inclusion criteria included 1) RCT study design; 2) patients 18 years of age or older with constipation associated with chronic opioid use due to chronic cancer pain, chronic non-cancer pain, or substance withdrawal; 3) a comparative trial of PEG versus either docusate sodium, sennosides or lactulose with doses described; 4) participants could be inpatients, outpatients or palliative care patients; 5) primary efficacy outcomes of frequency of bowel movements and quality of stool and secondary outcomes assessing adverse effects, drug interactions, use of additional laxatives and relief of symptoms associated with constipation. Using these criteria, none of the 2,158 citations found were eligible.[19] The review is helpful to comprehend the paucity of head-to-head comparative data for drugs commonly used to manage OIC.

Another systematic review with more lenient inclusion criteria of RCTs for management of OIC, including open-label RCTs and placebo-controlled trials, found evidence to support the use of PEG, lactulose, senna and the opioid-receptor antagonists (methylnaltrexone, naloxone, alvimopan) for the management of OIC. There was no evidence of difference between PEG, lactulose and senna, but PEG appears to be better tolerated. There is no evidence of benefit for bisacodyl (oral or rectal), docusate sodium, sodium phosphate enema, glycerin suppositories, mineral oil, magnesium salts or bulk-forming laxatives in the management of OIC.[20]

Efficacy of Pharmacological Therapies for the Treatment of Opioid-induced Constipation (2013)[3]:
Opioid-induced constipation may have significant implications. Surveys of patients receiving long-term opioid therapy reveal that OIC is associated with significant increases in physician visits and sickness-related absence from work, as well as significantly lower quality of life, compared to opioid users who do not experience constipation. This systematic review and meta-analysis assessed the efficacy of pharmacological therapies, compared with each other or with placebo, in OIC in terms of failure to respond to therapy. Of 1607 citations, 17 eligible studies, all placebo-controlled RCTs, were identified. Fourteen of the studies assessed mu-opioid receptor antagonists (4 used methylnaltrexone, 4 used naloxone and 4 used alvimopan), 2 studies assessed lubiprostone and 1 study assessed prucalopride (not approved in U.S.). No studies assessing linaclotide in OIC were identified. In total, 1261 (46.4%) of those assigned to a mu-opioid receptor antagonists failed to respond to therapy, compared to 886 (64.1%) of 1382 allocated to placebo. There was statistically significant heterogeneity between the studies (I^2=51%, p=0.01), which was confined to trials using methylnaltrexone. Patients receiving mu-opioid receptor antagonists experienced statistically significantly more adverse effects in the clinical trials than those who received placebo (60.6% vs. 53.5%, respectively; RR 1.11; 95% CI, 1.04 to 1.20; NNH 14). The primary adverse effects with these agents were diarrhea (RR 1.61; 95% CI, 1.21 to 2.13; NNH 33) and abdominal pain (RR 1.63; 95% CI, 1.06 to 2.51; NNH 20). In studies specifically evaluating methylnaltrexone, 553 (48.7%) patients who received the drug failed to respond to therapy, compared with 332 (64.5%) of 515 patients randomized to placebo. Studies ranged from 1 day to 12 weeks. There was statistically significant heterogeneity between studies (I^2=72%, p=0.003) owing to the wide range of doses studies and the disparate definitions of OIC and criteria for response utilized within each RCT. However, when only the 4 trials that used more than 2 days of therapy were analyzed, the RR of failure to respond to therapy was 0.79 (95% CI, 0.70 to 0.88) without significant heterogeneity (I^2=16%, p=0.25). In terms of individual adverse events, only diarrhea was significantly more common with methylnaltrexone (RR 1.94; 95% CI, 1.13 to 3.30; NNH 30). Studies of naloxone for OIC ranged from 3 to 12 weeks. There were 199 (44.2%) of the 450 patients assigned to naloxone who failed to respond to therapy compared to 244 (70.1%) of 348 patients allocated to placebo. Studies of alvimopan for OIC also ranged from 3 to 12 weeks. There were 529 (45.1%) of 1174 patients receiving alvimopan who failed to respond to therapy, compared to 310 (59.7%) of 519 patients randomized to placebo with no significant heterogeneity between studies (I^2=11%, p=0.34). A formal meta-analysis could not be conducted for lubiprostone in OIC since 1 of the 2 studies

was available only in abstract form and did not report raw outcomes data and multiple attempts to contact the corporate sponsor of these trials were unsuccessful. In one study, lubiprostone 24 mcg twice daily for 12 weeks was associated with a higher proportion of patients experiencing a first-dose spontaneous bowel movement within 48 hours compared to placebo (p=0.04). In the second study, 26.9% of patients receiving lubiprostone 24 mcg twice daily achieved 3 or more spontaneous bowel movements per week, for at least 9 of the 12 weeks studied, compared to 18.6% of patients who received placebo (p=0.035).[3] Relative risk of these agents are detailed in **table 7**.

Table 7. Failure to Respond to Therapy in Opioid-induced Constipation between mu-Opioid Receptor Antagonists and Placebo.

Drug	Relative Risk of Failure to Respond to Therapy vs. Placebo	Number Needed to Treat
Any mu-Opioid Receptor Antagonist*	0.69 (95% CI, 0.63 to 0.76)	4 (95% CI, 3 to 6)
Methylnaltrexone	0.67 (95% CI, 0.54 to 0.84)	3 (95% CI, 2 to 10)
Naloxone	0.64 (95% CI, 0.56 to 0.72)	4 (95% CI, 3 to 5)
Alvimopan	0.71 (95% CI, 0.65 to 0.78)	5 (95% CI, 4 to 11)

*methylnaltrexone, naloxone and alvimopan.

Treatment of Constipation in the Elderly (2013)[21]:
Consequences of constipation in older people who are frail can be substantial as excessive straining can trigger a syncope episode, or coronary or cerebral ischemia. In addition, case reports of older people identify stercoral ulceration, perforation and death as consequences of fecal impaction. Evidence from RCTs studying patients with chronic constipation and at least 65 years of age were eligible for this systematic review. Overall, evidence supports the use of osmotic laxatives as an effective treatment of chronic constipation in older people, whereas evidence supporting the use of bulk-forming laxatives, stool softeners and stimulant laxatives were lacking, limited or inconsistent. Four placebo-controlled RCTs of osmotic laxatives (n=250) all had statistically significant results favoring active treatment. One trial demonstrated PEG improved stool frequency and improvement in Rome III criteria in 57 patients with Parkinson's disease relative to placebo (80% vs. 30.4%, respectively; p=0.0012). Two trials demonstrated lactulose improved daily stool frequency over 12 weeks (0.63 ±0.31 for lactulose vs. 0.58 ±0.30 for placebo, p<0.02) and required less laxative use over 3 weeks relative to placebo (61% vs. 87%, respectively, p<0.02). The fourth trial showed that lactitol, another disaccharide similar to lactulose, increased stool frequency over 4 weeks relative to placebo (p<0.001). Bloating, flatulence, abdominal pain and diarrhea are common adverse events with osmotic laxatives, which may occur more often with lactulose because of its metabolism by colonic bacteria to carboxylic acids. Seven RCTs (n=254) were eligible in which older patients were randomly assigned to either dietary fiber or placebo. Two trials evaluating psyllium (n=20) did not show improvement in stool frequency. Two trials evaluating patients in nursing homes (n=182) compared stimulant laxatives with placebo. In one trial, senna resulted in 4.14 more BMs on average over 4 weeks versus placebo (p=0.017). The other study assessed an herbal formulation containing an anthraquinone combined with the osmotic laxative magnesium oxide. The formulation increased weekly frequency of BMs by 1 BM relative to placebo but did not affect global assessment of efficacy by caregivers. Bisacodyl has not been evaluated in RCTs in older patients. The authors also noted that regular use of stimulant laxatives may lead to decreased efficacy over time. One old trial conducted in 1968 has assessed stool softeners in older patients. In this trial, docusate sodium in 15 older patients improved constipation by increasing weekly bowel movements by 1 bowel movement relative to placebo (p<0.01). No RCTs assessing use of only enemas or suppositories to treat chronic constipation in older patients were identified.[21]

Effects of Linaclotide in patient with Chronic Constipation or in Patients with Irritable Bowel Syndrome with Constipation (2013)[22]:
The objective of this systematic review was to assess double-blind, placebo-controlled RCTs of linaclotide assessing CIC and IBS-C and to use meta-analysis to estimate the efficacy of linaclotide in treating the individual and combined end points of bowel function and abdominal symptoms. The primary outcomes assessed were the improvement from baseline in bowel symptoms, such as complete spontaneous bowel movements per week, or abdominal symptoms. A total

of 4 RCTs in IBS-C and 4 studies in CIC were eligible for inclusion. All authors on all studies included in the meta-analysis were employees or paid consultants for the developer and manufacturer of linaclotide. Heterogeneity was minimal in the CIC studies but it was significant in the IBS-C studies so a random effects model was chosen for analysis. Duration of treatment in the IBS-C trials ranged from 4 to 26 weeks. Linaclotide resulted in a pooled RR of response of 1.95 in the first 12 weeks (95% CI, 1.30 to 2.94) compared with placebo for IBS-C using the 290 mcg dose. This pooled estimate corresponded to a NNT of 7 (95% CI, 5 to 11). There were significantly more responders to linaclotide using the FDA standard definition of a responder in studies assessing constipation (≥3 SBM/week plus increase of ≥1 SBM/week from baseline in at least 75% of the weeks studied) with a RR of response of 3.20 (95% CI, 2.40 to 4.26) relative to placebo. There were also significantly more responders to linaclotide using the FDA standard definition of an abdominal pain responder in an IBS-C study (improvement in weekly average of daily worst abdominal pain of ≥30% from baseline for ≥75% of weeks) with a RR of response of 1.58 (95% CI, 1.76 to 5.49) relative to placebo. In the CIC trials, linaclotide had a RR of response of 4.26 (95% CI, 2.80 to 6.47) compared to placebo using the standard FDA definition of a responder in studies assessing constipation. This pooled estimate corresponded to a NNT of 7 (95% CI, 5 to 8). Both the 290 mcg dose and the 145 mcg dose resulted in similar efficacy. In all 8 trials, linaclotide was well tolerated with similar rates of adverse events as the placebo group. Of note, one of the authors of this review (Cremonini) was a Board member for the manufacturer of linaclotide (Ironwood/Forest) at the time of the writing.[22]

The Effects of Fiber in the Management of Chronic Idiopathic Constipation (2011)[23]:
Patients with CIC are often told to increase dietary fiber intake but the benefit if this treatment remains unclear. This systematic review identified only six RCTs out of 3146 citations assessing soluble and insoluble fiber supplementation using dichotomous data (to assess response to therapy) in the management of CIC against placebo or randomized trials comparing these therapies to no therapy. A formal meta-analysis was not performed due to concerns about the methodological quality of identified studies and risk of bias. Four eligible trials used soluble fiber; of these, three trials used psyllium and the fourth used a combination of inulin and maltodextrose. Two studies used insoluble fiber, wheat bran in one study and rye bread in the other. Duration of treatment ranged from 2 to 8 weeks. No trial was at low risk of bias, and the majority of trials were conducted in tertiary care centers and recruited mostly female patients. None of the trials allowed any active medications for the treatment of constipation to be co-administered to patients. The largest of the trials included in the review was a single-blind, placebo-controlled study (n=201) in which 86.5% of patients allocated to psyllium reported an improvement in symptoms compared to 47.4% of patients receiving placebo (P<0.001). This study also showed that psyllium reduced abdominal pain and discomfort in 80.0% of patients who reported those symptoms at baseline compared to 64.3% of those who received placebo (p=0.035). Straining on defecation was also reduced with psyllium compared to placebo (p=0.003). Smaller trials showed increased weekly bowel frequency and "normalization of evacuation" with psyllium relative to placebo. In addition, stool consistency and pain on defecation were also improved with psyllium, although straining and a sense of complete evacuation was not significantly different from placebo. Similar success relative to placebo was also observed with the soluble fiber mixture of inulin and maltodextrin when administered as a dairy preparation. When assessing insoluble fiber, bran did not have a significant impact on symptoms of constipation compared to placebo but rye bread did when compared to low fiber bread. One trial reported more abdominal pain in patients receiving psyllium compared to placebo and rye bread appeared to cause more GI side effects than low fiber bread. Otherwise, fiber was well tolerated in these studies.[23]

14

Guidelines:
The American Gastroenterological Association[2,24]:
The American Gastroenterological Association issued a technical statement and official recommendations on constipation in 2013.[2,24] Traditional approaches to treatment of constipation are recommended, starting with fiber supplementation, osmotic laxatives or stimulant laxatives, which are effective, safe and generally inexpensive, before newer agents are considered for management of chronic constipation.[2] The review notes that evidence shows these traditional approaches are as effective as newer agents for treating patients with chronic constipation. Grading of Recommendation Assessments, Development and

Evaluation (GRADE), which is based on the quality of evidence and magnitude of benefit, graded therapies into 4 categories (i.e., high, moderate, low or very low), and are summarized as follows[24]:

> *After discontinuing medications that can cause constipation and performing the recommended tests as guided by clinical features, a therapeutic trial of fiber supplementation and/or osmotic or stimulant laxatives is advised (strong recommendation, moderate-quality evidence). In most cases, constipation can be safely managed with long-term use of laxatives (strong recommendation, moderate-quality evidence). When bowel symptoms are refractory to traditional laxatives, new agents such as lubiprostone or linaclotide should be considered (weak recommendation, moderate-quality evidence). Suppositories or enemas rather than oral laxatives alone should be considered in patients with refractory pelvic floor dysfunction (weak recommendation, low-quality evidence).*

The evidence for specific treatment of chronic constipation and IBS-C adapted from the American Gastroenterological Association is summarized in **table 8**. Note the numbers in parenthesis reflect 95% confidence intervals where available. Data for therapeutic efficacy and numbers of patients with chronic constipation are obtained from meta-analyses.

Table 8. Comparison of Efficacy of Approved Therapies for Relief of Chronic Constipation and IBS-C.[2,24]

	Chronic Constipation			**IBS-C**		
Agent	NNT	n	GRADE Evidence	NNT	n	GRADE Evidence
Soluble Fiber	NA*	368	Very low	4.5	275	Moderate
Osmotic and Stimulant Laxatives	3 (2-4)	1411	High	NA	NA	Moderate**
PEG	2.4	573	High	NA	NA	Moderate**
Lubiprostone	4 (3-7)	610	Moderate	13	1171	Moderate
Linaclotide	6 (5-8)	2858	Moderate	10	420	Moderate

Abbreviations: n = number of patients; NA = not available; NNT = number needed to treat.

*Although some trials suggest that dietary fiber is effective in patients with chronic constipation, the efficacy cannot be estimated reliably because of quality of evidence.

**Although no controlled clinical trials have been conducted in patients with IBS-C, indirect evidence from trials in chronic constipation, the mechanism of action of these agents, and clinical experience suggest they are also likely to be effective in patients with IBS-C.

Several limitations of the evidence reviewed should be noted: endpoints differ across studies so strict comparisons are not advised; peripheral-acting opioid antagonists were not reviewed in the guideline so comparisons of these agents to traditional laxatives were not made; there is more evidence of efficacy in chronic constipation compared to IBS-C; there are no large high-quality studies of PEG, osmotic or stimulant laxatives in patients with IBS-C (though these agents are probably effective in IBS-C based on their pharmacology and clinical experience in patients with IBS-C); and the incremental utility of newer agents over traditional laxatives, which is the critical question in clinical practice, requires further study because refractoriness to traditional laxatives was not an entry criterion in most studies of newer agents. The evidence of efficacy is strongest for osmotic and stimulant laxatives but there are several well-designed clinical trials showing that lubiprostone and linaclotide are efficacious for patients with chronic constipation and in IBS-C but the upper bounds of the 95% confidence intervals, relative to placebo, were relatively low and generally imprecise.[2]

The World Gastroenterology Organization[25]:

The World Gastroenterology Organization published its Global Guideline on constipation in 2011.[25] In uncomplicated normal-transit constipation without alarm symptoms, the guidelines recommends a graded approach to treatment based on recommending changes in lifestyle and diet, stopping or reducing medications that cause constipation, and administering fiber supplementation or other bulk-forming agents. The second step is to add an osmotic laxative, of which the best evidence is for PEG, followed by lactulose. The third step in these patients should include stimulant laxatives and enemas. The guideline uses a resource-sensitive approach where recommendations are ranked according to the resources available.

If a diagnosis of slow-transit constipation has been made, an aggressive laxative program is recommended. In these patients, fiber, milk of magnesia and bisacodyl are recommended, followed by PEG, lactulose or lubiprostone if there is no improvement. **Table 9** summarizes the recommendation levels and grade of evidence of various pharmacological agents.[25]

Table 9. Recommendation Levels and Grades of Evidence for Common Treatment Modalities in Constipation.[25]

Treatment Modalities	Recommendation Level, Grade of Evidence*	Treatment Modalities	Recommendation Level and Grade of Evidence
Bulking Agents		Stimulant Laxatives	
Psyllium	Level 2, Grade B	Bisacodyl	Level 2, Grade B
Calcium polycarbophil	Level 3, Grade C	Senna	Level 3, Grade C
Methylcellulose	Level 3, Grade C		
Osmotic Laxatives		Others	
Polyethylene glycol	Level 1, Grade A	Lubiprostone	Level 1, Grade A
Lactulose	Level 2, Grade B	Linaclotide	Level 2, Grade B
Wetting Agents			
Docusate	Level 3, Grade C		

**methodology of grading the evidence and making recommendations is unclear. In short, Level 1 recommendation is higher than a Level 2 recommendation; Grade A evidence is more robust than Grade B evidence.*

National Institute for Health and Clinical Excellence (NICE)[26,27]:

The NICE recently published a quality standards for the treatment of constipation in children and young adults.[26,27] NICE recommends that children and young people with constipation receive a full assessment before a diagnosis of CIC is made to ensure that underlying causes or alarm symptoms are excluded. A diagnosis of CIC, in which the constipation cannot be explained by anatomical or physiological abnormalities, can only be made through a full assessment. Once the diagnosis of CIC has been made, NICE recommends children and young adults receive PEG as first-line treatment due to its effectiveness for treatment of constipation and ease administration at home and in the community. It is recommended to substitute a stimulant laxative with or without lactulose if PEG is not tolerated. Adding a stimulant laxative is advised if the treatment is ineffective after 2 weeks. The treatment should be reviewed by a healthcare professional within 6 weeks of starting therapy to assess effectiveness and adverse effects such fecal impaction or diarrhea. Maintenance with the laxative for several weeks may be advised once regular bowel habit has been established and may take several months. Stopping medication abruptly is not advised; rather, gradually reducing the dose over a period of months is recommended in respond to stool frequency and consistency. Parents or caregivers of children or young people starting laxative treatment should receive written information about laxatives to help enable self-management and adherence to therapy.[26]

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Appendix 1: Medications Associated with Constipation.

Class	Example	Class	Examples
5-HT3 receptor antagonists	*Ondansetron*	Bile acid sequestrants	*Cholestyramine*
Analgesics		Chemotherapy agents	
Opiates	*Oxycodone*	Vinca alkaloids	*Vincristine*
NSAIDs	*Ibuprofen*	Alkylating agents	*Cyclophosphamide*
Anticholinergic agents		Cation-containing compounds	
Tricyclic antidepressants	*Amitriptyline*	Aluminum	*Antacids*
Antiparkinsonian drugs	*Benztropine*	Calcium	*Antacids*
Antipsychotics	*Haloperidol*	Bismuth	
Antispasmodics	*Dicylcomine*	Iron supplements	*Ferrous sulfate*
Antihistamines	*Diphenhydramine*	Lithium	
Anticonvulsants	*Carbamazepine*	Endocrine medications	*Alendronate*
Antihypertensives			
Calcium channel blockers	*Verapamil*		
Diuretics	*Furosemide*		
Centrally-acting	*Clonidine*		
Beta-blockers	*Atenolol*		
Antiarrhythmics	*Amiodarone*		

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Appendix 2: Highlights of Prescribing Information for Prescription Products.[6,28–31]

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

MOVANTIK™ (naloxegol) tablets, for oral use
Initial US Approval: 2014

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

MOVANTIK (naloxegol) is an opioid antagonist indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain (1)

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

- Discontinue maintenance laxative therapy before starting MOVANTIK; may resume laxatives if patients have OIC symptoms after taking MOVANTIK for 3 days (2.1)
- Alteration in analgesic dosing regimen prior to starting MOVANTIK is not required (2.1)
- MOVANTIK has been shown to be efficacious in patients who have taken opioids for at least 4 weeks (2.1)
- Take on an empty stomach at least 1 hour prior to the first meal of the day or 2 hours after the meal (2.1)
- Swallow tablets whole, do not crush or chew (2.1)
- Avoid consumption of grapefruit or grapefruit juice (2.1, 7.1)
- Discontinue if treatment with the opioid pain medication is also discontinued (2.1)

Recommended dosage:

- 25 mg once daily; if not tolerated, reduce to 12.5 mg once daily (2.2)
- Renal Impairment (CLcr < 60 mL/min): 12.5 mg once daily; increase to 25 mg once daily if tolerated and monitor for adverse reactions (2.3, 8.6)

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

Tablets: 12.5 mg and 25 mg (3)

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

- Patients with known or suspected gastrointestinal obstruction and at increased risk of recurrent obstruction (4, 5.1)
- Concomitant use with strong CYP3A4 inhibitors (e.g., clarithromycin, ketoconazole) (4, 7.1)
- Known serious or severe hypersensitivity reaction to MOVANTIK or any of its excipients (4)

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

- Gastrointestinal perforation: Consider the overall risk benefit in patients with known or suspected lesions of the GI tract. Monitor for severe, persistent or worsening abdominal pain; discontinue if development of symptoms (5.1)
- Opioid withdrawal: Consider the overall risk benefit in patients with disruptions to the blood-brain barrier. Monitor for symptoms of opioid withdrawal (5.2)

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

The most common adverse reactions in clinical trials (≥3%) are: abdominal pain, diarrhea, nausea, flatulence, vomiting, and headache (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Moderate CYP3A4 inhibitors (e.g., diltiazem, erythromycin, verapamil): Increased naloxegol concentrations; avoid concomitant use; if unavoidable, reduce dosage to 12.5 mg once daily and monitor for adverse reactions (2.4, 7.1)
- Strong CYP3A4 inducers (e.g., rifampin): Decreased concentrations of naloxegol; concomitant use is not recommended (7.1)
- Other opioid antagonists: Potential for additive effect and increased risk of opioid withdrawal; avoid concomitant use (7.1)

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

- Pregnancy: May precipitate opioid withdrawal in a fetus (8.1)
- Nursing Mothers: Discontinue drug or nursing taking into consideration importance of drug to mother (8.3)
- Hepatic Impairment: avoid in severe impairment (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 01/2015

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HIGHLIGHTS OF PRESCRIBING INFORMATION

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

RELISTOR (methylnaltrexone bromide) Subcutaneous Injection
Initial U.S. Approval: 2008

RECENT MAJOR CHANGES

Indications and Usage, Opioid-Induced Constipation in Adult Patients with Chronic Non-Cancer Pain (1.1)	[09/2014]
Dosage and Administration, Important Administration Information (2.1)	[09/2014]
Dosage and Administration, Opioid-Induced Constipation in Adult Patients with Chronic Non-Cancer Pain (2.2)	[09/2014]
Contraindications (4)	[09/2014]
Warnings and Precautions, Gastrointestinal Perforation (5.1)	[09/2014]
Warnings and Precautions, Opioid Withdrawal (5.3)	[09/2014]

INDICATIONS AND USAGE

RELISTOR is an opioid antagonist indicated for:

- Treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain (1.1)
- Treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient.

  Limitation of Use: Use beyond four months has not been studied (1.2)

DOSAGE AND ADMINISTRATION

- For subcutaneous use only (2.1)
- Inject in upper arm, abdomen or thigh. Rotate injection sites (2.1)
- Be within close proximity to toilet facilities once administered (2.1)
- Discontinue if treatment with opioid pain medication is also discontinued (2.1)

Opioid-induced constipation in adult patients with chronic non-cancer pain:

- RELISTOR has been shown to be efficacious in patients who have taken opioids for at least 4 weeks (2.1)
- Discontinue maintenance laxative therapy before starting RELISTOR; may resume laxatives if patients have OIC symptoms after taking RELISTOR for 3 days (2.1)
- Recommended dosage: 12 mg subcutaneously once daily (2.2)

Opioid-induced constipation in adult patients with advanced illness:

- Recommended one dose administered every other day, as needed, but no more frequently than one dose in a 24-hour period (2.1, 2.3)

Weight of Adult Patient	Subcutaneous Dose*
Less than 38 kg	0.15 mg/kg
38 kg to less than 62 kg	8 mg
62 kg to 114 kg	12 mg
More than 114 kg	0.15 mg/kg

* see full prescribing information for corresponding injection volume

- Severe renal impairment (Clcr <30 mL/min): Reduce dose by one-half (2.4)
- Prescribe pre-filled syringes only for patients requiring an 8 mg or 12 mg dose (2.5)

DOSAGE FORMS AND STRENGTHS

Single-use vial (3)

- 12 mg/0.6 mL solution for subcutaneous injection, for use with a 27 gauge x ½-inch needle and 1 mL syringe
- 12 mg/0.6 mL solution for subcutaneous injection with one 1 mL syringe with retractable 27 gauge x ½-inch needle, two alcohol swabs

Single-use pre-filled syringe (3)

- 8 mg/0.4 mL solution for subcutaneous injection
- 12 mg/0.6 mL solution for subcutaneous injection

CONTRAINDICATIONS

- Patients with known or suspected mechanical gastrointestinal obstruction and at increased risk of recurrent obstruction (4, 5.1)

WARNINGS AND PRECAUTIONS

- Gastrointestinal perforation: Consider the overall risk benefit in patients in patients with known or suspected lesions of the GI tract. Monitor for severe, persistent or worsening abdominal pain; discontinue if development of symptoms (5.1)
- Severe or persistent diarrhea: Discontinue if severe or persistent diarrhea occurs during treatment (5.2)
- Opioid withdrawal: Consider the overall risk benefit in patients with disruptions to the blood-brain barrier. Monitor closely for symptoms of opioid withdrawal (5.3)

ADVERSE REACTIONS

- The most common adverse reactions (≥ 1%) in adult patients with opioid-induced constipation and chronic non-cancer pain are abdominal pain, nausea, diarrhea, hyperhidrosis, hot flush, tremor, and chills (6.1)
- The most common adverse reactions (≥ 5%) in adult patients with opioid-induced constipation and advanced illness are abdominal pain, flatulence, nausea, dizziness, and diarrhea (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Salix Pharmaceuticals Inc. at 1-800-508-0024 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Other opioid antagonists: Potential for additive effect and increased risk of opioid withdrawal; avoid concomitant use (7.1)

USE IN SPECIFIC POPULATIONS

- Pregnancy: May precipitate opioid withdrawal in a fetus (8.1)
- Nursing Mothers: Discontinue drug or nursing, taking into consideration importance of drug to mother (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 09/2014

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

AMITIZA (lubiprostone) capsules, for oral use
Initial U.S. Approval: 2006

RECENT MAJOR CHANGES

Indications and Usage (1.2)	04/2013
Dosage and Administration (2.1)	04/2013
Warnings and Precautions, Pregnancy (5.1)	removed 11/2012

INDICATIONS AND USAGE

Amitiza is a chloride channel activator indicated for:

- Treatment of chronic idiopathic constipation in adults (1.1)
- Treatment of opioid-induced constipation in adults with chronic, non-cancer pain (1.2)
- Treatment of irritable bowel syndrome with constipation in women ≥ 18 years old (1.3)

Limitations of Use:

Effectiveness of Amitiza in the treatment of opioid-induced constipation in patients taking diphenylheptane opioids (e.g., methadone) has not been established (1) (14.2)

DOSAGE AND ADMINISTRATION

Capsules should be swallowed whole and should not be broken apart or chewed (2)

Chronic Idiopathic Constipation and Opioid-induced Constipation

- 24 mcg taken twice daily orally with food and water (2.1)

Reduce the dosage in patients with moderate and severe hepatic impairment (2.1)

Irritable Bowel Syndrome with Constipation

- 8 mcg taken twice daily orally with food and water (2.2)

Reduce the dosage in patients with severe hepatic impairment (2.2)

DOSAGE FORMS AND STRENGTHS

- Capsules: 8 mcg and 24 mcg (3)

CONTRAINDICATIONS

- Amitiza is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction. (4)

WARNINGS AND PRECAUTIONS

- Patients may experience nausea; concomitant administration of food may reduce this symptom (5.1)
- Do not prescribe for patients that have severe diarrhea (5.2)
- Patients taking Amitiza may experience dyspnea within an hour of first dose. This symptom generally resolves within 3 hours, but may recur with repeat dosing (5.3)
- Evaluate patients with symptoms suggestive of mechanical gastrointestinal obstruction prior to initiating treatment with Amitiza (5.4)

ADVERSE REACTIONS

- Most common adverse reactions (incidence > 4%) in chronic idiopathic constipation are nausea, diarrhea, headache, abdominal pain, abdominal distension, and flatulence (6.1)
- Most common adverse reactions (incidence > 4%) in opioid-induced constipation are nausea and diarrhea (6.1)
- Most common adverse reactions (incidence > 4%) in irritable bowel syndrome with constipation are nausea, diarrhea, and abdominal pain (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals at 1-877-825-3327 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Concomitant use of diphenylheptane opioids (e.g., methadone) may interfere with the efficacy of Amitiza (7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm (8.1)
- Nursing Mothers: Caution should be exercised when administering to a nursing woman (8.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: April 2013

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ENTEREG® (alvimopan) capsules, for oral use
Initial U.S. Approval: 2008

WARNING: POTENTIAL RISK OF MYOCARDIAL INFARCTION WITH LONG-TERM USE: FOR SHORT TERM HOSPITAL USE ONLY

See full prescribing information for complete boxed warning.

- **Increased incidence of myocardial infarction was seen in a clinical trial of patients taking alvimopan for long-term use. (5.1)**
- **ENTEREG is available only through a restricted program for short-term use (15 doses) called the ENTEREG Access Support and Education (E.A.S.E.®) Program. (5.1, 5.2)**

RECENT MAJOR CHANGES

Boxed Warning	10/2013
Indications and Usage (1)	10/2013
Warnings and Precautions (5)	10/2013

INDICATIONS AND USAGE

ENTEREG is an opioid antagonist indicated to accelerate the time to upper and lower gastrointestinal recovery following surgeries that include partial bowel resection with primary anastomosis. (1)

DOSAGE AND ADMINISTRATION

12 mg administered 30 minutes to 5 hours prior to surgery followed by 12 mg twice daily beginning the day after surgery for up to 7 days for a maximum of 15 in-hospital doses. (2)

DOSAGE FORMS AND STRENGTHS

Capsules: 12 mg (3)

CONTRAINDICATIONS

Patients who have taken therapeutic doses of opioids for more than 7 consecutive days prior to taking ENTEREG (4)

WARNINGS AND PRECAUTIONS

- A higher number of myocardial infarctions was reported in patients treated with alvimopan 0.5 mg twice daily compared with placebo in a 12-month study in patients treated with opioids for chronic non-cancer pain, although a causal relationship with long-term use has not been established. (5.1)
- Patients recently exposed to opioids are expected to be more sensitive to the effects of ENTEREG and therefore may experience abdominal pain, nausea and vomiting, and diarrhea. (5.3)
- Not recommended in patients with severe hepatic impairment. (5.4)
- Not recommended in patients with end-stage renal disease. (5.5)
- Not recommended in patients with complete gastrointestinal obstruction or in patients who have surgery for correction of complete bowel obstruction. (5.6)
- Not recommended in pancreatic or gastric anastomosis. (5.7)

ADVERSE REACTIONS

The most common adverse reaction (incidence ≥1.5%) occurring with a higher frequency than placebo among ENTEREG-treated patients undergoing surgeries that included a bowel resection was dyspepsia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Cubist Pharmaceuticals, Inc., at 1-877-282-4786 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Hepatic impairment:
  - Severe: ENTEREG is not recommended. (8.6)
  - Mild-to-moderate: Does not require dosage adjustment, but should monitor for adverse reactions. (8.6)
- Renal impairment:
  - End-Stage: Has not been studied and is not recommended. (8.7)
  - Mild-to-Severe: Dosage adjustment is not required, but should monitor for adverse reactions. (8.7)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2013

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

LINZESS (linaclotide) capsules, for oral use
Initial U.S. Approval: 2012

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

LINZESS is contraindicated in pediatric patients up to 6 years of age; linaclotide caused deaths due to dehydration in young juvenile mice. Avoid use of LINZESS in pediatric patients 6 through 17 years of age. The safety and efficacy of LINZESS has not been established in pediatric patients under 18 years of age (4, 5.1, 8.4, 13.2).

----------**RECENT MAJOR CHANGES**----------

Boxed Warning	7/2014
Contraindications (4)	7/2014
Warnings and Precautions, Pediatric Risk (5.1)	7/2014
Warnings and Precautions, Diarrhea (5.2)	7/2014

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

LINZESS is a guanylate cyclase-C agonist indicated in adults for treatment of:

- Irritable bowel syndrome with constipation (IBS-C) (1.1)
- Chronic idiopathic constipation (CIC) (1.2)

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

- IBS-C: Take 290 mcg orally once daily (2.1)
- CIC: Take 145 mcg orally once daily (2.2)
- Take on empty stomach at least 30 minutes prior to first meal of the day (2.1, 2.2)

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

Capsules: 145 mcg and 290 mcg (3)

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

- Pediatric patients under 6 years of age (4)
- Patients with known or suspected mechanical gastrointestinal obstruction (4)

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

- *Diarrhea:* Patients may experience severe diarrhea. Hold or stop LINZESS (5.2)

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

Most common adverse reactions (incidence of at least 2%) reported in IBS-C or CIC patients are diarrhea, abdominal pain, flatulence and abdominal distension. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Forest Pharmaceuticals, Inc., at 1- 800- 678-1605 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: July, 2014

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Drug Safety:

Black Boxed Warnings:

ENTEREG (alvimopan)[6]:

WARNING: POTENTIAL RISK OF MYOCARDIAL INFARCTION WITH LONG-TERM USE: FOR SHORT-TERM HOSPITAL USE ONLY

- **Increased incidence of myocardial infarction was seen in a clinical trial of patients taking alvimopan for long-term use.**
- **ENTEREG is available only through a restricted program for short-term use (15 doses) called the ENTEREG Access Support and Education Program.**

LINZESS (linaclotide)[29]:

WARNING: PEDIATRIC RISK

- **LINZESS is contraindicated in pediatric patients up to 6 years of age; linaclotide caused deaths due to dehydration in young juvenile mice. Avoid use of LINZESS in pediatric patients 6 through 17 years of age. The safety and efficacy of LINZESS has not been established in pediatric patients under 18 years of age.**

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Appendix 3: Comparative Efficacy, Safety, Pharmacology and Pharmacokinetic Properties of Naloxegol and Methylnaltrexone.

Summary of Pivotal Studies for Drugs with New FDA-Approved Indications.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Quality Rating/ Internal Validity Risk of Bias/ Applicability Concerns
1. Chey, et al.[32] Phase 3 (Study 04) MC, DB, PG, RCT	1. Naloxegol 25 mg once daily (N25) 2. Naloxegol 12.5 mg once daily (N12.5) 3. Placebo once daily (P) Duration: 12 weeks All laxatives and bowel therapy (e.g., prune juice, herbals) prohibited during study. Rescue laxative limited to bisacodyl 10-15 mg, followed by enema if needed, if no BM in 72 h. Stratification ensured ≥50% subjects in each arm had inadequate response to laxative(s) prior to study.	Demographics: Age: ~52 y Female: ~60% White: ~77% Opioid (morphine-equiv): ~140 mg/d Pain Type: back (56%); arthritis/joint/fibromyalgia (18.1%) Key Inclusion Criteria: ●Adults on daily stable morphine equivalent of 30-1000 mg/d for ≥4 weeks for non-cancer pain ●Opioid-induced constipation (<3 SBM/week w/ ≥1 of the following symptoms in ≥25% BMs 4 weeks before screening: hard/lumpy stool; straining; sensation of incomplete evacuation; or anorectal obstruction Key Exclusion Criteria: ●Uncontrolled pain ●Medications or medical conditions causing constipation or diarrhea ●Conditions assoc. w/ increased BBB permeability	ITT: P: 214 N12.5: 213 N25: 214 Attrition: P: 36 N12.5: 37 N25: 41	**Primary Endpoint:** Response Rate = ≥3 SBM/week and increase of ≥1 SBM/week from baseline for ≥9/12 weeks and ≥3 of final 4 weeks of study (*SBM=BM w/o use of rescue laxative in previous 24h*). P: 29.4% N12.5: 40.8% N25: 44.4% N12.5 RR 1.38 (95% CI, 1.06 to 1.80); p=0.02 N25 RR 1.51 (95% CI, 1.17 to 1.95); p=0.001 Key Secondary Endpoint: Response rate in patients with inadequate response to laxatives before study: P: 28.8% N12.5: 42.6% N25: 48.7% N12.5 RR 1.48 (95% CI, 1.04 to 2.11); p=0.03 N25 RR 1.69 (95% CI, 1.21 to 2.37); p=0.002	11.4%/9 15%/7 13.8%/8 19.9%/5	Attrition due to AE: P: 5.6% N12.5: 4.3% N25: 10.3% Abdominal pain: P: 3.3% N12.5: 8.5% N25: 12.6% MACE: P: 0 N12.5: 0.5% (n=1, MI) N25: 0.5% (n=1, MI) Mean Δ opioid dose from baseline: P: -1.8 mg/d N12.5: -2.3 mg/d N25: 0.4 mg/d Mean Δ pain score (0-10): P: -0.2 N12.5: -0.3 N25: -0.2	NA	**Quality Rating**: **FAIR** **Internal Validity (Risk of Bias)**: Selection: randomization occurred centrally w/ adequate concealment of allocation. Performance: Double-dummy design described. Detection: Data blinded from study team; imputation of missing data unclear; not truly ITT as data on some subjects not included. Attrition: twice as many patients dropped out in 25 mg group vs. 12.5 mg group due to AE. **Applicability**: Patient: age, sex and race of subjects typical for Oregon; opioid dose also typical. Intervention: prohibiting laxatives during study limit applicability and comparison to "usual care" (i.e., laxatives); short duration of study limits safety data, unclear if tachyphylaxis develops long-term. Comparator: adequate comparison groups Outcomes: clinically relevant outcomes assessed using validated tools, but limited due to short duration. Setting: outpatients only; data retrieved primarily from patient diaries. **Analysis**: Study funded, designed, monitored, and data analysis supervised by AstraZeneca. Other pre-specified secondary endpoints of unknown clinical significance included time to first post-dose SBM and number of days per week with at 1-3 SBMs during week 1-12.

2. Chey, et al.[32] Phase 3 (Study 05) MC, DB, PG, RCT	See Study 04	Demographics: Age: ~52 y Female: ~63% White: ~80% Opioid (morphine-equiv): ~136 mg/d Pain Type: back (56.8%); arthritis/joint/fibromyalgia (21.6%) Key Inclusion Criteria: See Study 04 Key Exclusion Criteria: See Study 04	ITT: P: 232 N12.5: 232 N25: 232 Attrition: P: 44 N12.5: 53 N25: 59	**Primary Endpoint:** Response Rate = ≥3 BM/week and increase of ≥1 BM/week from baseline for ≥9/12 weeks and ≥3 of final 4 weeks of study P (29.3%) N12.5 (34.9%) N25 (39.7%) N12.5 RR 1.19 (95% CI, 0.91 to 1.55); p=0.2 (NS) N25 RR 1.35 (95% CI, 1.05 to 1.74); p=0.02 Key Secondary Endpoint: Response rate in patients with inadequate response to laxatives before study: P (31.4%) N12.5 (42.4%) N25 (46.8%) N12.5 RR 1.35 (95% CI, 0.97 to 1.88); p=0.07 (NS) N25 RR 1.49 (95% CI, 1.08 to 2.06); p=0.01	 NA 10.4%/10 NA 15.4%/7	Attrition due to AE: P: 5.2% N12.5: 5.2% N25: 10.3% Abdominal pain: P: 7.8% N12.5: 10.9% N25: 19.0% MACE: P: 0.9% (n=2, MI) N12.5: 0 N25: 0 Mean Δ opioid dose from baseline: P: -0.3 mg/d N12.5: -1.3 mg/d N25: 0.1 mg/d Mean Δ pain score (0-10): P: -0.1 N12.5: -0.1 N25: 0	NA	**Quality Rating**: **FAIR** **Internal Validity (Risk of Bias)**: See Study 04. **Applicability**: See Study 04. **Analysis**: Lack of statistical significance in the efficacy endpoint for the 12.5 mg dose relative to placebo suggests reserving 12.5 mg dose for patients who cannot tolerate the 25 mg dose (e.g., due to abdominal paint, etc.) See Study 04 for other comments.

3. Webster, et al.[33] Phase 3 MC, OL, PG, R	1. Naloxegol 25 mg once daily (N) 2. Usual Care (UC) Duration: 52 weeks Laxatives or bowel regimens prohibited in the naloxegol arm. Rescue laxative in naloxegol arm limited to bisacodyl 10-15 mg, followed by enema if needed, if no BM in 72 h. Included 90% new patients and 10% rollover patients from Study 04 and Study 05.	Demographics: Age: ~53 y Female: ~66% White: ~78% Opioid (morphine-equiv): ~146 mg/d Benzodiazepines: 41.4% Antidepressants: 31.1% Key Inclusion Criteria: ●Adults on daily stable morphine equivalent of 30-1000 mg/d for non-cancer pain ● Opioid-induced constipation (<3 SBM/week w/ ≥1 of the following symptoms in ≥25% BMs during 4-week screening: Bristol stool scale stool type 1 or 2; moderate, severe or very severe straining; or incomplete BM. Key Exclusion Criteria: ●0 BMs or uneven distribution of SBMs (0 in one week with ≥4 following week) during 2-week screening period ●Inadequate response to laxatives during screening ●Uncontrolled pain ●Medications or medical conditions causing constipation or diarrhea ●Conditions assoc. w/ increased BBB permeability	Enrolled: N: 563 UC: 281 Safety Analysis: N: 534 UC: 270 Attrition: N: 207 UC: 81	**Safety and Tolerability (all AEs assessed):** Study Completion: N 58.1% vs. UC 67.3% Any AE: N 81.8% vs. UC 72.2% Serious AE: N 9.6% vs. UC 11.1% Deaths: N (n=1) vs. UC (n=1), neither considered related to study drug AEs leading to study discontinuation of naloxegol: 10.5% Top Treatment-emergent AEs: Abdominal Pain: N 17.8% vs. UC 3.3% Diarrhea: N: 12.9% vs. UC 5.9% Nausea: N: 9.4% vs. UC 4.1% Back Pain: N 9.0% vs. UC 8.9% Headache: N 9.0% vs. UC 4.8% Flatulence: N 6.9% vs. UC 1.1% ECG Assessments: not reported in results Major Adverse Cardiovascular Events (MACE) (cardiovascular death, nonfatal MI and nonfatal stroke): N (n=2) vs. UC (n=2), neither considered related to study drug Opioid Withdrawal: N (n=2) vs. UC (n=0) Bowel Perforation: N (n=0) vs. UC (n=0) Δ Opioid Requirements (morphine equivalents): N -1.2 to -5.7 mg/d vs. UC -2.7 vs -5.3 mg/d Δ Pain Score (0-10): N ≤0.4 points vs. UC ≤0.4 points Median weekly bisacodyl dose for naloxegol patients: 1.1 mg randomization to month 1; 0 mg from month 1 to month 12.	NA	**Quality Rating**: **FAIR** **Internal Validity (Risk of Bias)**: Selection: internal computer-generated randomization scheme Performance: no blinding; no control Detection: unclear if data analyses blinded; imputation of missing data unclear Attrition: higher attrition in 52-week study vs. 12-week study more typical of real world experience. **Applicability**: Patient: subjects w/ inadequate response to laxatives not randomized. Intervention: approximates real world experience Comparator: Uncontrolled w/ usual care Outcomes: all AEs reported Setting: outpatient clinics; usual care arm was observational without intervention by investigators **Analysis**: Study funded, designed, monitored, and data analysis supervised by AstraZeneca (drug sponsor). Quality of study based on the study intent not to evaluate efficacy/effectiveness, but to assess real-world adverse effects of naloxegol (e.g., cardiovascular events). However, outcomes primarily patient-reported at monthly intervals, which are subject to recall bias. Nonetheless, serious adverse events such as rare cardiovascular signals were not observed with naloxegol.

4. Michna, et al.[34] Phase 3 MC, DB, PG, RCT	1. Methyl-naltrexone 12 mg SC once daily (QD) 2. Methyl-naltrexone 12 mg SC QOD (QOD) 3. Placebo SC once daily (P) Duration: 4 weeks DB followed by 8 weeks OL. Patients discontinued all laxatives prior to study. Only bisacodyl tablets (1 oral dose, up to 4 tablets) permitted as rescue laxative if no BM x3 d.	Demographics: Age: ~49 y Female: 60.2% White: 89.8% Opioid (morphine-equiv): ~159 mg/d Key Inclusion Criteria: ●Adults with chronic nonmalignant pain for ≥2 months on opioids for ≥1 month w/ avg morphine equivalent >50 mg/day for ≥2 weeks ●<3 BMs occurring w/o use of laxative in the prior 24 h per week w/ ≥1 of the following symptoms: hard/lumpy stool; straining; sensation of incomplete evacuation Key Exclusion Criteria: ●h/o inflammatory bowel disease in last 6 months ●Bowel impaction or bowel obstruction ●h/o rectal bleed (not hemorrhoids/fissures) ●h/o malignancy in last 5 y ●h/o chronic constipation before starting opioids	mITT: QD: 150 QOD: 148 P: 162 Attrition: QD: 28 QOD: 28 P: 16	**Primary Endpoints:** 1. Proportion of patients w/ RFBM w/i 4 h of first dose in study: QD: 33.3% (p<0.001 vs. P) QOD: 35.1% (p<0.001 vs. P) P: 9.9% *(95% CI or SD not provided)* 2. Percentage of active injections per patient resulting in RFBM w/i 4 h: QD: 28.9% (p<0.001 vs. P) QOD: 30.2% (p<0.001 vs. P) P: 9.4% *(95% CI or SD not provided)*	 23.4%/5 25.2%/4 19.5%/6 20.8%/5	Attrition due to AE: QD: 6.7% QOD: 8.8% P: 2.5% Serious AE: QD: 1.7% QOD: 3.3% P: 0.7% Treatment emergent AE: QD: 49.3% QOD: 45.3% P: 38.3% Abdominal pain: QD: 19.3% QOD: 15.5% P: 3.7% Pain scores: Not reported. "No statistical or clinical significant difference" Opioid Withdrawal: Not reported. "No statistical or clinical significant difference" Rescue Laxative Use: QD: 38.7% (p<0.001 vs. P) QOD: 49.3% (p=0.03 vs. P) P: 61.7%	NA	**Quality Rating**: **FAIR** **Internal Validity (Risk of Bias)**: Selection: clear method of randomization with adequate concealment of allocation. Performance: method of double-blinding, maintaining blinding described. Detection: group allocation unblinded to investigators for data analysis; true ITT not performed but analysis methods appropriate. Attrition: overall attrition higher for treatment arms but low overall rates. **Applicability**: Patient: age, sex and race of subjects typical for Oregon; opioid dose also typical. Intervention: prohibiting laxatives during study limit applicability and comparison to "usual care" (i.e., laxatives); short duration of study limits applicability of data, unclear if tachyphylaxis develops long-term. Comparator: adequate comparison groups. Outcomes: clinical significance of primary outcomes questionable. Setting: not described, but presumed outpatient clinics. **Analysis**: Most authors employees of and stockholders of Wyeth. Study funded by drug sponsor. Quality of study based on lack of details regarding open label data assessment and questionable significance of primary outcomes. Pre-specified secondary endpoints were statistically significant for the two treatment arms relative to placebo, which included time to first RFBM after injection, change in weekly number of RFBMs, and improvement in Bristol Stool Form Scale scores, straining, and completeness of evacuation.

Abbreviations [alphabetical order]: AE = adverse event; ARR = absolute risk reduction; BB = blood brain barrier; BM = bowel movement; CI = confidence interval; d = days; DB = double-blind; h = hours; h/o = history of; ITT = intention to treat; MACE = major adverse cardiovascular events; MC = multi-centered; 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; NS = not statistically significant; OIC = opioid-induced constipation; OL = open label; PG = parallel group; PP = per protocol; QOD = every other day; QoL = quality of life; R = randomized; RCT = randomized controlled trial; RFBM = rescue-free bowel movement; SBM = spontaneous bowel movement; SC = subcutaneously; SD = standard deviation; w/ = with; w/i = within; y = years.

*Quality of each study is ranked as "Good", "Fair" or "Poor" based on DURM Standard Methods for Quality Assessment and Grading the Evidence.
Note: number needed to treat in all cases in this review is rounded up to the next whole person.

Comparative Pharmacology and Pharmacokinetic Properties of Naloxegol and Methylnaltrexone.[30,31]

Drug Name	Naloxegol	Methylnaltrexone
Mechanism of Action	A peripheral antagonist of the mu-opioid receptor. It is a PEGylated derivative of naloxone and a substrate for P-gp transporter which reduces its passive permeability versus naloxone. Penetration into the central nervous system is thus negligible.	A peripheral antagonist of the mu-opioid receptor. It is a quaternary amine, which restricts its ability to cross the blood brain barrier and enter the central nervous system.
Pharmacokinetic Properties • Cmax • Dose-proportional Cmax and AUC • Distribution • Half-life • Metabolism • Renal Excretion • Fecal Excretion	 • <2 hours; secondary peak 0.4-3 hours later • Yes • 4.2% protein bound; Vd = 968-2140 L • 6-11 hours • Liver via CYP3A • 16% • 68%	 • 30 minutes • Yes • 11-15% protein bound; Vd = 1.1 L/kg • 8 hours • 44% (not through CYP pathways) • 54% • 17%

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Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 1946 to November Week 3 2014
1 lubiprostone.mp. 280
2 exp Constipation/ or exp Laxatives/ 13620
3 linaclotide.mp. 123
4 alvimopan.mp. 143
5 methylnaltrexone.mp. 314
6 naloxegol.mp. 5
7 1 or 2 or 3 or 4 or 5 or 6 14024
8 limit 7 to (meta analysis or systematic reviews) 380
9 limit 8 to english language 341

Appendix 5: Suggested Prior Authorization Criteria
Author: A. Gibler, Pharm.D. Date: March 2015

Drugs for Constipation

Length of Authorization:

Up to 6 months

Not Covered by OHP:

- Disorders of function of stomach and other functional digestive disorders which includes constipation and Irritable Bowel Syndrome

(ICD-9: 536.0-536.3, 536.8-536.9, 537.1-537.2, 537.5-537.6, 537.89-537.9, 564.0-564.6, 564.89-564.9, 787.60, 787.61, 787.63, 839.40)

Requires PA:

- Non-preferred drugs

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is the diagnosis covered by the OHP?	Yes: Go to 3	No: Pass to RPh. Deny; diagnosis not covered by OHP.
3. Will the prescriber consider a change to a preferred product? Message: preferred products do not require a PA.	Yes: Inform prescriber of covered alternatives	No: Go to 4

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Approval Criteria		
4. Has the patient failed a 2-week trial of at least 3 of the following management strategies due to lack of effectiveness, contraindications or adverse effects? **A** Dietary modification—increased dietary fiber (25 g/day) **B** Bulk-forming Laxatives: (psyllium [e.g,. Metamucil],methylcellulose [e.g., Citrucel], calcium carbophil [e.g., Fibercon]) **C** Saline Laxatives: (magnesium hydroxide [e.g., Milk of Magnesia], magnesium citrate, sodium phosphate [Fleet Enema]) **D** Stimulant Laxatives: (senna or bisacodyl) **E** Osmotic Laxatives: (lactulose, sorbitol or polyethylene glycol 3350 [e.g., Miralax, Glycolax])	Yes: Approve for 6 months.	No: Pass to RPh. Go to 5.
5. RPh only: Constipation is not covered under the OHP. Therefore, funding for drugs that treat constipation are dependent whether the constipation adversely affects, or is secondary to, the underlying medical condition covered by the Prioritized List. • Alvimopan (ENTEREG): FDA labeling, including a black boxed warning for risk of myocardial infarction, limit use to *in hospital use only* for a maximum of 15 doses. Evidence is primarily for the immediate post-operative period only. • Linaclotide (LINZESS): Constipation secondary to irritable bowel syndrome is not approvable. Chronic constipation caused by a funded condition or adversely affecting a funded condition is approvable if medically appropriate and justification is provided for not meeting criterion #4. • Lubiprostone (AMITIZA): Constipation secondary to irritable bowel syndrome or opioid-induced constipation is not approvable. Chronic constipation caused by a funded condition or adversely affecting a funded condition is approvable if medically appropriate and justification is provided for not meeting criterion #4. • Methylnaltrexone (RELISTOR): Opioid-induced constipation in patients with non-cancer pain is not approvable. Chronic constipation secondary to continuous opioid use as part of a palliative care regimen is approvable if justification is provided for not meeting criterion #4. • Naloxegol (MOVANTIK): Opioid-induced constipation in patients with non-cancer pain is not approvable. Justification must be provided for not meeting criterion #4.		

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P&T / DUR Action: 3/15 (AG); 3/09 (KK)
Revisions: 1/15
Initiated: 7/09

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Literature Scan: Oral Antiepileptic Drugs

Month/Year of Review: March 2015

Date of Last Review: May 2014
Source Document: OSU College of Pharmacy

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

Current Prior Authorization Criteria:
See **Appendix 5**.

Conclusions:

- There were no new comparative systematic reviews or evidence-based guidelines of antiepileptic drugs (AEDs) identified on which to recommend changes to the PDL class.
- FDA expanded the black-boxed warnings on valproate products to include possible fetal neural tube defects and other structural abnormalities (e.g., craniofacial defects, cardiovascular malformations, hypospadias, limb malformations) when used during pregnancy.
- There is insufficient evidence that controlled-release carbamazepine is more effective than the immediate-release formulations; however, low quality evidence suggests the controlled-release formulations may be more tolerable.
- There is insufficient evidence that felbamate is effective as add-on therapy for refractory partial-onset epilepsy.
- There is moderate quality evidence that tiagabine is effective at reducing seizure frequency but is associated with more dizziness, fatigue, nervousness and tremor when used as add-on therapy in patients with localization-related seizures who have failed at least two AEDs as monotherapy.
- There is moderate quality evidence that in the short term, adding pregabalin at doses ranging from 150-600 mg per day to AED therapy can significantly reduce seizure rates and cease seizures altogether in patients with drug-resistant partial epilepsy. There is insufficient evidence, however, for longer treatment duration and insufficient evidence comparing pregabalin against other adjunctive treatments.
- There is moderate quality evidence that in the short term, adding topiramate at doses no greater than 300 mg per day to AED therapy can significantly reduce rates and cease seizures altogether in patient with drug-resistant partial epilepsy. There is insufficient evidence, however, for longer treatment duration and insufficient evidence comparing topiramate against other adjunctive treatments.

Recommendations:

- Sunset PA criteria for pregabalin and replace with current PA criteria for non-funded pain conditions presented at this meeting (see **Appendix 5**).
- Remove PA criteria for preferred topiramate products due to cost effectiveness (see **Appendix 5**).
- No further review or research needed at this time. Review comparative drug costs in the executive session.

1

Previous Conclusions and Recommendations:

- There were no new comparative systematic reviews or evidence-based guidelines identified on which to recommend changes to the current PDL class.
- FDA safety communications indicate that all valproate products are now contraindicated for pregnant women and ezogabine has a new Boxed Warning about the risk of permanent retinal abnormalities, vision loss and skin discoloration with its use.
- There is insufficient comparative efficacy and safety evidence for eslicarbazepine versus other AEDs.
- There is high level of evidence eslicarbazepine is associated with overall >50% reduction in seizure frequency (RR 1.86 95% CI 1.46-2.36) over placebo when added on to current therapy for drug-resistant partial epilepsy but patients on eslicarbazepine were more likely to withdraw for adverse events (RR 2.26 95% CI 0.98 to 5.21).
- Maintain eslicarbazepine as non-preferred.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to placebo or active controls were conducted. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Dynamed, 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 drugs, indications, and safety alerts. Finally, the AHRQ National Guideline Clearinghouse 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.

A summary of potentially relevant trials are available in **Appendix 2**. Abstracts of these trials are available in **Appendix 3**.

New Systematic Reviews:

Efficacy of Antiepileptic Drugs for Secondary Prevention of Seizures after Stroke

A Cochrane Review performed by Sykes, et al.[1] assessed the effects of antiepileptic drugs (AEDs) for the primary and secondary prevention of seizures after stroke. Eligible studies were randomized and quasi-randomized controlled trials in which patients were assigned to treatment or control group (placebo or no drug). Only one trial fulfilled study inclusion criteria: a prospective, randomized, double-blind, placebo-controlled trial comparing valproic acid to placebo for primary prevention of seizures in 72 adults with spontaneous non-aneurysmal, non-traumatic intracerebral hemorrhage. No statistically significant difference in the primary outcome of seizure occurrence at one year was found between the groups. However, the treatment group had a lower, non-statistically significant incidence of early seizures (less than 14 days after onset of hemorrhage) compared to the placebo group. The valproic acid treatment group also demonstrated a statistically significant benefit in the secondary outcome of National Institutes of Health Stroke Scale (NIHSS) score at one year compared to the placebo group. This supports the hypothesis of a neuroprotective/neuro-remodeling effect of valproic acid. Whether these results can be translated to apply to other forms of stroke (e.g. ischemic, subarachnoid hemorrhage) is not certain. There is insufficient evidence to support the routine use of AEDs for the primary and secondary prevention of seizures after stroke.[1]

Immediate-release vs. Controlled-release Carbamazepine formulations

A Cochrane Review performed by Powell, et al.[2] assessed the efficacy of immediate-release carbamazepine (IR CBZ) versus controlled-release carbamazepine (CR CBZ) in patients diagnosed with epilepsy. Eligible studies were RCTs comparing IR CBZ to CR CBZ in patients initiating monotherapy and patients treated with IR CBZ but experiencing unacceptable adverse events. Primary outcomes measured included seizure frequency, incidence of adverse events, proportion with treatment failure and quality of life measures. Ten trials were identified: one trial included patients with newly diagnosed epilepsy and nine trials included patients on treatment with IR CBZ. Eight trials assessing seizure frequency had conflicting results with heterogeneous measures; and only one trial reported a statistically significant reduction in seizures with CR CBZ relative to IR CBZ. Nine trials reported measures of adverse events. There was a trend in favor of CR CBZ with four trials showing statistically significant reduction in adverse events compared to IR CBZ. Two trials reported fewer adverse events with CR CBZ but the difference was not significant. One trial found no difference, and one trial reported more adverse events with CR CBZ but the difference was not significant. There is insufficient evidence to support using CR CBZ over IR CBZ for preventing seizures; however, CR CBZ may be associated with fewer adverse events when compared to IR CBZ and may be an acceptable alternative to patients who are experiencing unacceptable adverse effects from IR CBZ but otherwise have adequate seizure control.[2] The included trials were of small size, poor methodological quality and at high risk of bias, limiting the validity of the conclusions found in the review.

Efficacy of Antiepileptic Drugs as Add-on Therapy

A Cochrane Review performed by Shi, et al.[3] assessed the efficacy and tolerability of felbamate versus placebo when used as an add-on therapy for patients with refractory partial-onset epilepsy. Eligible studies were double-blind, single-blind or open-label randomized placebo-controlled add-on studies of patients of any age with refractory partial-onset seizures. Outcomes measured included 50% or greater reduction in seizure frequency; absolute or percentage reduction in seizure frequency; treatment withdrawal; adverse events; and quality of life. Only three RCTs with a total of 153 subjects were included in the review but due to significant methodological heterogeneity, clinical heterogeneity and differences in outcome measures, a meta-analysis of the results was not possible. None of the studies reported a 50% reduction in seizure frequency and only one study reported absolute and percentage reduction in seizure frequency compared to placebo (34.4 seizures/8 weeks vs. 40.2 seizures/8 weeks, respectively; p=0.046). Adverse effects rates were higher with felbamate than with placebo, particularly headache, nausea and dizziness.[3]

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A Cochrane Review performed by Pulman, et al.[4] assessed the effects of tiagabine as add-on treatment in patients with drug-resistant localization-related seizures. Eligible studies were double-blind, single-blind or open-label randomized, placebo or active-controlled add-on trials of patients of any age with localization-related seizures in which an adequate method of concealment of randomization was used. Outcomes measured included 50% or greater reduction in seizure frequency; treatment withdrawal during the study period; adverse effects, cognitive effects; quality of life. Four parallel-group and two cross-over group trials were included. The overall risk ratio (RR) for a 50% or greater reduction in seizure frequency (tiagabine vs. placebo) was 3.16 (95% CI, 1.97 to 5.07) but because of differences in response rates among trials, regression models were unable to provide reliable estimates of response to individual doses. The RR for treatment withdrawal was 1.81 for tiagabine (95% CI, 1.25 to 2.62). Tiagabine was associated with a significant increase in dizziness, fatigue, nervousness and tremor but without difference in cognition or quality of life outcomes.[4]

A second Cochrane Review performed by Pulman, at al.[5] assessed the efficacy and tolerability of pregabalin when used as add-on therapy for drug-resistant partial epilepsy. Eligible studies were RCTs comparing pregabalin with placebo or an alternative AED in patients with drug-resistant partial epilepsy. Outcomes measured included 50% or greater reduction in seizure frequency; seizure freedom (defined as absolute cessation of seizure activity during the study period); treatment withdrawal for any reason during the study period; treatment withdrawal for adverse events; and nature of adverse events. Six industry-sponsored

(n=2009) placebo-controlled studies of short duration (12 weeks) were identified and included in the analysis. Doses of pregabalin studied ranged from 50 mg per day to 600 mg per day. The overall RR for a 50% or greater reduction in seizure frequency (pregabalin vs. placebo) was 2.61 (95% CI, 1.70 to 4.01) with efficacy demonstrated at doses ranging from 150 mg per day to 600 mg per day and odds of response doubling from 300 mg per day to 600 mg per day (OR 2.12; 95% CI, 1.76 to 2.54). Pregabalin was also associated with complete cessation of seizure activity during the study period (RR 2.59; 95% CI, 1.05 to 6.36). Patients were significantly more likely to have withdrawn treatment for any reason with pregabalin than placebo (RR 1.39; 95% CI, 1.13 to 1.72) or for adverse effects (RR 2.69; 95% CI, 1.88 to 3.86). Ataxia, dizziness, somnolence and weight gain were all significantly associated with use of pregabalin. The authors rated the risk of bias as low or unclear due to possibility of publication bias.[5]

A third Cochrane Review performed by Pulman, et al.[6] assessed the efficacy and tolerability of topiramate when used as add-on therapy for patients with drug-resistant partial epilepsy. Eligible studies were RCTs comparing topiramate with placebo or an alternative AED in patients with drug-resistant partial epilepsy. Outcomes measured included 50% or greater reduction in seizure frequency; seizure freedom (defined as absolute cessation of seizure activity during the study period); treatment withdrawal for any reason during the study period; and adverse events. Eleven trials (n=1401) were included, with double-blind phases ranging from 11 to 19 weeks. The overall RR for a 50% or greater reduction in seizure frequency (topiramate vs. placebo) was 2.97 (95% CI, 2.38 to 3.72) with an increasing effect at higher doses, though without any advantage at doses over 300 mg per day. Topiramate was also associated with complete cessation of seizure activity during the study period (RR 3.41; 95% CI, 1.37 to 8.51). Patients were significantly more likely to have withdrawn treatment for any reason with topiramate than placebo (RR 2.44; 95% CI, 1.64 to 3.62). Difficulty concentrating, dizziness, fatigue, paresthesia, somnolence, 'thinking abnormally' and weight loss were all significantly associated with use of topiramate. Evidence of publication bias was found and risk of bias was rated as low or unclear.[6]

New Guidelines:
None.

New FDA Drug Approvals:
None.

New Formulations/Indications:
Rufinamide (BANZEL) received an expanded indication from the FDA in February 2015 for adjunctive treatment of seizures associated with Lennox Gastaut Syndrome in children 1 year of age and older and adults. Previously, the indication was for children 4 years of age and older and adults. Approval was based on a single open-label, active-controlled (rufinamide 45 mg/kg/day (n=25) vs. adjunctive AED of investigator's choice (n=11)), randomized, pharmacokinetic bridging study. The pharmacokinetic profile of rufinamide was not significantly affected by age either as a continuous covariate (1 to 35 years) or a categorical covariate (age categories: 1 to less than 4 years and 4 years of age and older), after body weight was taken into consideration. The adverse reaction profile observed in the rufinamide-treated patients occurred at a rate similar as in earlier trials of children 4 years of age and older and adults. Adverse reactions that occurred in at least 2 patients (8%) treated with rufinamide with higher frequency than the comparator group were: vomiting (24%), somnolence (16%), bronchitis (12%), constipation (12%), cough (12%), decreased appetite (12%), rash (12%), otitis media (8%), pneumonia (8%), decreased weight (8%), gastroenteritis (8%), nasal congestion (8%) and pneumonia aspiration (8%).[7]

New FDA Safety Alerts:

Valproate

In January 2015, WARNINGS AND PRECAUTIONS labeling for valproate received new information[8]:

> Birth defects [BLACK BOXED WARNING]: valproate is associated with possible neural tube defects and other structural abnormalities (e.g., craniofacial defects, cardiovascular malformations, hypospadias, limb malformations) when used during pregnancy.
>
> Bleeding and other hematopoietic disorders: valproate is associated with dose-related thrombocytopenia. Valproate use has also been associated with decreases in other cell lines and myelodysplasia. Because of reports of cytopenias, inhibition of the secondary phase of platelet aggregation, and abnormal coagulation parameters (e.g., low fibrinogen, coagulation factor deficiencies, acquired von Willebrand's disease), measurements of complete blood counts and coagulation tests are recommended before initiating therapy and at periodic intervals.
>
> Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan hypersensitivity reaction: DRESS has been reported in patients taking valproate and may be fatal or life-threatening.

References:

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2. Powell G, SaundersM,Marson AG. Immediate-release versus controlled-release carbamazepine in the treatment of epilepsy. Cochrane Database of Systematic Reviews 2014, Issue 2. Art. No.: CD007124. DOI: 10.1002/14651858.CD007124.pub3.

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4. Pulman J, Hutton JL, Marson AG. Tiagabine add-on for drug-resistant partial epilepsy. Cochrane Database of Systematic Reviews 2014, Issue 2. Art. No.: CD001908. DOI: 10.1002/14651858.CD001908.pub3.

5. Pulman J, Hemming K, Marson AG. Pregabalin add-on for drug-resistant partial epilepsy. Cochrane Database of Systematic Reviews 2014, Issue 3. Art. No.: CD005612. DOI: 10.1002/14651858.CD005612.pub3.

6. Pulman J, Jette N, Dykeman J, Hemming K, Hutton JL,Marson AG. Topiramate add-on for drug-resistant partial epilepsy. Cochrane Database of Systematic Reviews 2014, Issue 2. Art. No.: CD001417. DOI: 10.1002/14651858.CD001417.pub3.

7. Banzel (rufinamide) [product information]. Woodcliff Lake, NJ: Eisai Inc., February 2015.

8. Center for Drug Evaluation and Research Webpage. Food and Drug Administration. http://www.fda.gov/Drugs/default.htm. Accessed February 13, 2015.

Appendix 1: Current Status on Preferred Drug List

Preferred		Non-Preferred	
GENERIC NAME	**FORM**	**GENERIC NAME**	**FORM**
CARBAMAZEPINE	ORAL SUSP	CARBAMAZEPINE	CPMP 12 HR
CARBAMAZEPINE	TAB CHEW	CLOBAZAM	ORAL SUSP
CARBAMAZEPINE	TAB ER 12H	CLOBAZAM	TABLET
CARBAMAZEPINE	TABLET	DIAZEPAM	RECTAL KIT
DIAZEPAM	RECTAL KIT	EZOGABINE	TABLET
DIVALPROEX	CAP SPRINK	ESLICARBAZEPINE	TABLET
DIVALPROEX	TAB ER 24H	EZOGABINE	TABLET
DIVALPROEX	TAB DR	FELBAMATE	ORAL SUSP
ETHOSUXIMIDE	CAPSULE	FELBAMATE	TABLET
ETHOSUXIMIDE	SOLUTION	GABAPENTIN	SOLUTION
ETHOTOIN	TABLET	GABAPENTIN	TABLET
GABAPENTIN	CAPSULE	LACOSAMIDE	SOLUTION
LACOSAMIDE	TABLET	LAMOTRIGINE	TAB ER 24H
LAMOTRIGINE	TABLET	LAMOTRIGINE	TAB RAPIDIS
LEVETIRACETAM	SOLUTION	LAMOTRIGINE	TB CHW DSP
LEVETIRACETAM	TABLET	LAMOTRIGINE	TB ER DSPK
METHSUXIMIDE	CAPSULE	LAMOTRIGINE	TB RD DSPK
OXCARBAZEPINE	ORAL SUSP	LEVETIRACETAM	TAB ER 24H
OXCARBAZEPINE	TABLET	OXCARBAZEPINE	TAB ER 24H
PHENOBARBITAL	ELIXIR	PERAMPANEL	TABLET
PHENOBARBITAL	TABLET	PREGABALIN	CAPSULE
PHENYTOIN	ORAL SUSP	PREGABALIN	SOLUTION
PHENYTOIN	TAB CHEW	RUFINAMIDE	ORAL SUSP
PHENYTOIN EXTENDED	CAPSULE	TOPIRAMATE	CAP ER 24H
PRIMIDONE	TABLET	TOPIRAMATE	CAP SPRINK
RUFINAMIDE	TABLET	VALPROIC ACID	CAPSULE DR
TIAGABINE	TABLET	VIGABATRIN	POWD PACK
TOPIRAMATE	TABLET	VIGABATRIN	TABLET
VALPROIC ACID	CAPSULE		
VALPROIC ACID	SOLUTION		
ZONISAMIDE	CAPSULE		

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Appendix 2: New Clinical Trials

One hundred and five potentially relevant clinical trials were evaluated from the literature search. After further review, 102 trials were not head-to-head RCTs and were therefore excluded. The remaining 3 trials are briefly described in the table below. Full abstracts are included in **Appendix 3**. The Medline search strategy is presented in **Appendix 4**.

Table 1: Description of Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Rossetti, et al. Pragmatic, OL, Phase 2 RCT 2 sites Duration 1 year	• Levetiracetam titrated up to 1500 mg BID vs. • Pregabalin titrated up to 300 mg BID *Flexible dosing*	Adults w/ primary brain tumor (WHO grades II-IV) provoking ≥1 seizure episode.	Composite endpoint of: • Status epilepticus • 2 seizures w/ impaired consciousness • Need of 2nd AED • Need to d/c study drug (lack of effectiveness or adverse events)	• Levetiracetam 36% • Pregabalin 44% Note: composite primarily driven by need for 2nd AED with pregabalin users.
Baulac, et al. MC, DB, RCT Extension study of a Phase 3 trial	• Zonisamide 200-500 mg Qday* vs. • Carbamazepine 200-600 mg BID* *Flexible dosing*	Patients who completed Phase 3 trial seizure-free and willing to maintain seizure diary and report AEs	Retention rate, defined as the proportion of patients remaining in the extension study at each visit for tin ITT population.	• Zonisamide 87.6% • Carbamazepine 84.8% Note: reason for extension study was to assess tolerability, for which both drugs were tolerated well. Discontinuation due to AE was rare.
Zaccara, et al. MC, DB, PG, NI, RCT	• Levetiracetam titrated up to 1500 mg BID vs. • Pregabalin titrated up to 300 mg bid *Used as adjunctive therapy w/ flexible dosing*	Adults w/ epilepsy with partial seizures inadequately controlled with 2-4 AEDs other than pregabalin or levetiracetam	Responder rate, defined as proportion of patients w/ ≥50% reduction in 28-day seizure rate (all partial seizures) over 12-week maintenance phase, as compared with baseline.	• Levetiracetam 58.8% • Pregabalin 59.1% Note: Lower bound of 95% CI was -8.0%, which was greater than the pre-specified noninferiority margin of -12.0%. Thus, pregabalin was noninferior to levetiracetam.

Abbreviations: AE = adverse event; AED = antiepileptic drug; CI = confidence interval; DB = double blind; ITT = intention to treat; MC = multi-centered; NI = non-inferiority design; OL = open label; PG = parallel group; RCT = randomized controlled trial; WHO = World Health Organization.

Rossetti A, Jeckelmann S, Novy J, et al. Levetiracetam and pregabalin for antiepileptic monotherapy in patients with primary brain tumors. A phase II randomized study. *Neuro-Oncology*. 2014;16:584-588.

Background. In patients with brain tumors, the choice of antiepileptic medication is guided by tolerability and pharmacokinetic interactions. This study investigated the effectiveness of levetiracetam (LEV) and pregabalin (PGB), 2 non-enzyme-inducing agents, in this setting.
Methods. In this pragmatic, randomized, unblinded phase II trial (NCT00629889), patients with primary brain tumors and epilepsy were titrated to a monotherapy of LEV or PGB. Efficacy and tolerability were assessed using structured questionnaires. The primary composite endpoint was the need to discontinue the study drug, add-on of a further antiepileptic treatment, or occurrence of at least 2 seizures with impaired consciousness during 1 year follow-up.
Results. Over 40 months, 25 patients were randomized to LEV, and 27 to PGB. Most were middle-aged men, with a high-grade tumor and at least one generalized convulsion. Mean daily doses were 1125 mg (LEV) and 294 mg(PGB). Retention rates were 59% in the LEV group, and 41%in the PGB group. The composite endpoint was reached in 9 LEV and 12 PGB patients—need to discontinue: side effects, 6 LEV, 3 PGB; lack of efficacy, 1 and 2; impaired oral administration, 0 and 2; add-on of another agent: 1 LEV, 4 PGB; and seizures impairing consciousness: 1 in each. Seven LEV and 5 PGB subjects died of tumor progression.
Conclusions. This study shows that LEV and PGB represent valuable monotherapy options in this setting, with very good antiepileptic efficacy and an acceptable tolerability profile, and provides important data for the design of a phase III trial.

Baulac M, Patten A, Giorgi L. Long-term safety and efficacy of zonisamide versus carbamazepine monotherapy for treatment of partial seizures in adults with newly diagnosed epilepsy: results of a phase III, randomized, double-blind study. *Epilepsia*. 2014;55:1534-1543.

Objective: To investigate the long-term safety and maintenance of efficacy of monotherapy with once-daily zonisamide versus twice-daily controlled-release carbamazepine for partial seizures in adults with newly diagnosed epilepsy.
Methods: Long-term, double-blind, extension study, conducted in patients completing a phase III noninferiority trial comparing zonisamide and carbamazepine monotherapy. Patients continued their randomized treatment, with dosing adjusted according to tolerability/response (zonisamide 200–500 mg/day; carbamazepine 400–1,200 mg/day). Safety assessments included treatment-emergent adverse events (TEAEs) and clinical laboratory parameters. Efficacy assessments included retention rate and the proportion of patients remaining seizure free for ≥24 months.
Results: Overall, 120 (87.6%) of 137 patients randomized to zonisamide and 134 (84.8%) of 158 patients randomized to carbamazepine completed the study. More than three-fourths of patients were exposed to >24 months of treatment. For zonisamide versus carbamazepine, incidences were similar for TEAEs (52.6% vs. 46.2%), serious treatment-related TEAEs (0.7% vs. 1.9%), and TEAEs leading to withdrawal (1.5% vs. 0.6%). The incidence of treatment-related TEAEs was 26.3% for zonisamide compared with 19.6% for carbamazepine, and the most frequently reported treatment-related TEAEs were decreased weight (5.1% vs. 0%), decreased appetite (3.6% vs. 0%), memory impairment (2.9% vs. 3.2%), and decreased hemoglobin level (1.5% vs. 3.2%). Most TEAEs were of mild or moderate intensity. There were no reports of Stevens-Johnson syndrome or toxic epidermal necrolysis in either group. Zonisamide was associated with small-to-moderate decreases in bicarbonate levels from baseline (mean 3.4 mM). There were no reports of metabolic acidosis. Retention rates were generally similar between treatment groups at all time points throughout the extension study. The proportion of patients remaining seizure free for ≥24 months was also similar for zonisamide (32.3%) and carbamazepine (35.2%).
Significance: Once-daily zonisamide monotherapy demonstrated favorable long-term safety and maintenance of efficacy in treating partial seizures in adults with newly diagnosed epilepsy. No new or unexpected safety findings emerged.

Zaccara G, Almas M, Pitman V, et al. Efficacy and safety of pregabalin versus levetiracetam as adjunctive therapy in patients with partial seizures: a randomized, double-blind, noninferiority trial. *Epilepsia*. 2014;55:1048-1057.

Objectives: To assess the comparative efficacy and safety of pregabalin and levetiracetam for the reduction of seizure frequency in patients with partial seizures.
Methods: This was a randomized, double-blind, flexible-dose, parallel-group noninferiority study of pregabalin and levetiracetam (randomized 1:1) as adjunctive treatment in adult patients with refractory partial seizures. The study included a 6-week baseline phase, 4-week dose-escalation phase, and 12-week maintenance phase. The primary endpoint was the proportion of patients with a ≥50% reduction in 28-day seizure rate during the 12-week maintenance phase, as compared with baseline. Noninferiority of pregabalin was declared if the lower limit of the 95% confidence interval (CI) for the difference in responder rates was greater than the prespecified noninferiority margin of 12%. A key secondary endpoint was the percent change from baseline in 28-day seizure rate during the dose-escalation and maintenance phases.
Results: Five hundred nine patients were randomized to pregabalin (n = 254) or levetiracetam (n = 255) and 418 (208 pregabalin, 210 levetiracetam) completed the maintenance phase. With both pregabalin and levetiracetam, the proportion of patients with a ≥50% reduction in 28-day seizure rate was 0.59 (difference between groups, 0.00 [95% CI, -0.08 to 0.09]). Because the lower bound of the 95% CI was greater than the prespecified noninferiority margin of 12%, pregabalin was not inferior to levetiracetam. There was no significant difference between pregabalin and levetiracetam in the percent change in 28-day seizure rate (median difference, 4.1 [95% CI,2.6 to 10.9], p = 0.3571). In a post hoc analysis, the proportion of patients who were seizure-free for the maintenance phase was lower with pregabalin (8.4%) than with levetiracetam (16.2%), p = 0.0155. Safety profiles were similar and consistent with prior trials.
Significance: These results indicate that pregabalin is noninferior, and has a similar tolerability, to levetiracetam as adjunctive therapy in reducing seizure frequency in patients with partial seizures.

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to February Week 2 2015

1 exp Epilepsy, Partial, Motor/ or exp Epilepsy, Temporal Lobe/ or exp Epilepsy, Complex Partial/ or exp Epilepsy, Partial, Sensory/ or exp Epilepsy, Reflex/ or exp Epilepsy, Benign Neonatal/ or exp Epilepsy, Tonic-Clonic/ or exp Epilepsy, Post-Traumatic/ or exp Epilepsy, Absence/ or exp Epilepsy, Frontal Lobe/ or exp Epilepsy/ or exp Epilepsy, Rolandic/ or exp Myoclonic Epilepsy, Juvenile/ or exp Epilepsy, Generalized/ 69190
2 exp Seizures/ 20691
3 1 or 2 69371
4 exp Carbamazepine/ 4987
5 exp Diazepam/ 4190
6 exp Valproic Acid/ 6627
7 exp Ethosuximide/ 245
8 ethotoin.mp. 2
9 gabapentin.mp. 4122
10 lacosamide.mp. 333
11 lamotrigine.mp. 3660
12 levetiracetam.mp. 1812
13 methsuximide.mp. 17
14 oxcarbazepine.mp. 1218
15 exp Phenobarbital/ 2849
16 exp Phenytoin/ 2907
17 clobazam.mp. 335
18 ezogabine.mp. 228
19 ESLICARBAZEPINE.mp. 113
20 felbamate.mp. 455
21 perampanel.mp. 76
22 pregabalin.mp. 1663
23 rufinamide.mp. 136
24 topiramate.mp. 3233
25 exp Vigabatrin/ 952
26 exp Anticonvulsants/ 48264
27 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 53710
28 3 and 27 18433
29 limit 28 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or pragmatic clinical trial or randomized controlled trial or systematic reviews) 3963
30 limit 29 to (english language and yr="2014 -Current") 105

Clobazam (Onfi®)

Goal(s):

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

Length of Authorization:

- 12 months

Requires PA:

- Non-preferred drugs
- Clobazam (Onfi®)

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Does the client have a diagnosis of Lennox-Gastaut syndrome and is 2 years of age or older?	Yes: Go to #3.	No: Pass to RPH; Deny (medical appropriateness)
3. Is the patient uncontrolled on current baseline therapy with at least one other antiepileptic medication?	Yes: Approve for 12 months.	No: Pass to RPH; Deny (medical appropriateness)

Limitations of Use:

• Clobazam is not indicated for other epilepsy syndromes other than Lennox-Gastaut.

DUR / P&T Action: *3/15; 5/12 (MH)*
Revision(s):
Initiated: *8/20/12*

Topiramate

Goal(s):

- Approve topiramate only for covered diagnoses (above the line) which are supported by the medical literature (e.g. Epilepsy, and migraine prophylaxis).

Length of Authorization:

90 days to lifetime

Requires PA:

- ~~Clients >18 years old~~Non-preferred topiramate products

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Does ~~client~~the patient have a diagnosis of epilepsy (ICD-9 code 345.0-345.9, 780.39, or 907.0)?	Yes: Approve for lifetime (until 12-31-2036)	No: Go to #3
3. Does the ~~client~~patient have a diagnosis of migraine (ICD-9 346)?	Yes: Approve for 90 days with subsequent approvals dependent on documented positive response for lifetime*	No: Go to #4
4. Does the client have a diagnosis of bipolar affective disorder or schizoaffective disorder? • ICD-9 296 and subsets • ICD-9 295 and subsets	Yes: Go to #5	No: Go to #6

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Approval Criteria		
5. Has the client tried or are they contraindicated to at least two of the following drugs: • Lithium • Valproate and derivatives • Lamotrigine • Carbamazepine • Atypical antipsychotic Document drugs tried or contraindications.	Yes: Approve for 90 days with subsequent approvals dependent on documented positive response for lifetime approval.*	No: Pass to RPH; Deny, (Medical Appropriateness) and recommend trial of covered alternative.
6. Is the client using the medication for weight loss? (Obesity ICD9 278.0, 278.01)?	Yes: Pass to RPH; Deny, (Not covered by the OHP)	No: Go to #7.
7. Pass to RPH. All other indications need to be evaluated for appropriateness: • Neuropathic pain • Post-Traumatic Stress Disorder (PTSD) • Substance abuse	Use is off-label: Deny, (Medical Appropriateness), other treatments should be tried as appropriate. Below the line diagnoses: Deny (Not covered by the OHP) If clinically warranted: Deny, yesterday's date (Medical Appropriateness) and use clinical judgment to approve for 1 month starting today to allow time for appeal. MESSAGE: "Although the request has been denied for long term use because it is considered medically inappropriate, it has also been APPROVED for one month to allow time for appeal."	

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P&T / DUR Action: *3/15, 2/12, 9/07, 11/07*
Revision(s): *5/12, 1/12*
Initiated: *1/11*

Pregabalin (Lyrica®)

*****SUNSET AND REPLACE WITH NEW PA CRITERIA FOR NON-FUNDED PAIN CONDITIONS*****

Goal(s):

- Cover pregabalin only for above-the-line diagnoses that are supported by the medical literature (e.g. Epilepsy, diabetic neuropathy, post-herpetic neuralgia).
- Pregabalin has not demonstrated superiority to other first-line treatments for neuropathic pain and its use should be reserved for treatment failure.

Length of Authorization:

90 days to lifetime (criteria specific)

Requires PA:

- Non-preferred drugs
- Pregabalin (Lyrica®)

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org
- Anxiety: SSRIs, TCAs, Benzodiazepines, Buspirone
- Neuropathic pain: TCAs, Tramadol, Carbamazepine, Gabapentin capsules

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Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Does client have diagnosis of epilepsy? (ICD-9 code 345.0-345.9, 780.39, or 907.0)	Yes: Approve for lifetime (until 12-31-2036)	No: Go to #3.
3. Does the client have rheumatism, unspecified or fibrositis, fibromyalgia/ myalgia or myositis or below the line neuralgia/neuritis? (729.0, 729.1 or 729.2)	Yes: Pass to RPH; Go to #7.	No: Go to #4.

Approval Criteria		
4. Does client have diagnosis of one the following? • Diabetic neuropathy (ICD9: 250.6 & subsets) – Document diabetic therapy (supporting meds) • Post-herpetic neuralgia (ICD9: 053 & subsets) • Trigeminal and other above the line neuralgias (ICD9 350, 352)	Yes: Go to #5.	No: Go to #6.
5. Has the client tried or are they contraindicated to gabapentin capsules AND one of the following? • TCAs • Carbamazepine Document drugs tried or contraindications.	Yes: Approve for 90 days with subsequent approvals dependent on documented* positive response for lifetime (12-31-2036) *Documented response means that follow-up and response is noted in client's chart per clinic staff	No: Pass to RPH; Deny, (Medical Appropriateness) and recommend trial of covered alternative.
6. Does the client have an anxiety disorder (ICD9 300xx)	Yes: Go to #7.	No: Go to #8.
7. Has the client tried or are they contraindicated to at least two of the following drug classes? • SSRIs • TCAs • Benzodiazepines • Buspirone Document drugs tried.	Yes: Approve for 90 days with subsequent approvals dependent on documented* positive response for lifetime (12-31-2036) approval.	No: Pass to RPH; Deny, (Medical Appropriateness) and recommend trial of covered alternative.

Approval Criteria

8. Pass to RPH
    - For Bipolar affective disorder: there is no data to support its use for this indication, (Deny Medical Appropriateness) recommend other alternatives (lithium, valproate, carbamazepine, lamotrigine)

    - For Migraine prophylaxis: there is no data to support its use for this indication, (Deny Medical Appropriateness) recommend other alternatives (beta-blockers, calcium channel blockers, valproate, gabapentin, TCAs) Refer to American Academy of Neurology Guideline http://www.neurology.org/cgi/reprint/55/6/754.pdf

    - If clinically warranted, may DENY yesterday's date (Medical Appropriateness) and use clinical judgment to APPROVE for 1 month starting today to allow time for appeal.

    MESSAGE: "Although the request has been denied for long term use because it is considered medically inappropriate, it has also been APPROVED for one month to allow time for appeal."

    All other indications need to be evaluated to see if diagnosis is above or below the line:

    - Above the line neuropathies found in table 1 (list is not all inclusive) may be approved for 90 days with subsequent approvals dependent on documented positive response. (Documented response means that follow-up and response is noted in client's chart per clinic staff)

    **** Also, see footnote.**

    - Below the line neuropathies such as those found in table 2 (list is not all inclusive) that are related to above the line diagnoses found in table 3 may be approved for 90 days with subsequent approvals dependent on documented positive response. (Documented response means that follow-up and response is noted in client's chart per clinic staff).

    **** Also, see footnote.**

    Below the line diagnoses should be: **Denied, (Not covered by the OHP).**

    **** Forward any neuropathy/neuralgia ICD-9 codes not found in the Table 1 to the Lead Pharmacist. These codes will be forwarded to DMAP for consideration.**

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Table 1 – Examples of other above the line neuropathies

ICD-9	Description
337.0	Idiopathic Peripheral autonomic neuropathy
354.2	Ulner nerve lesion
356 – 356.9	Hereditary and idiopathic peripheral autonomic neuropathy
357.89, 357.9	Inflamatory Polyneuropathy
723.4	Brachial neuritis or radiculitis
724.4	Thoracic or Lumbosacral neuritis or radiculitis unspecified

Table 2 – Examples of below the line diagnosis that can be approved ONLY if it's due to a condition that is found in Table 3

ICD-9	Description
337.2	Reflex sympathetic dystrophy
337.3	Autonomic Dysreflection
724.3	Sciatia –Neuralgia or neuritis of sciatic nerve
729.1	Myalgia Myositis
729.2	Neuralgia/Neuritis and Radiculitis Unspecified

Table 3 – Above the line condition that can be the basis of below the line neuropathy found in Table 2

ICD-9	Above the line Condition
336.9	Unspecified disease of spinal cord
340	Multiple sclerosis
344.0	Quadraplegia
344.1	Paraplegia
754.2	Scoleosis
737.3	Kyphoscolosis
907.0	Late effects of injuries to nervous system

P&T / DUR Action: *3/15; 9/07; 11/07*
Revision(s): *1/11*
Initiated: *4/08*

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
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Literature Scan: Topical Corticosteroids

Month/Year of Review: March 2015

Date of Last Review: March 2013
Source Document: OSU College of Pharmacy

Current Status of PDL Class: See Appendix 1.

Conclusions and Recommendations:

- Select preferred agents based on comparative costs in executive session.
- At least one agent in each of the potency categories (Appendix 1) should be preferred.
- No further review or research needed.

Previous Conclusions and Recommendations:

- Evidence does not support a difference in efficacy/effectiveness.
- Evidence does not support a difference in harms/adverse events.
- Consider covering at least one representative from each potency group.

Methods:
A Medline literature search for new systematic reviews and head-to-head randomized controlled trials (RCTs) assessing clinically relevant outcomes were conducted. The Medline search strategy used for this literature scan is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Dynamed, 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 drugs, indications, and safety alerts. Finally, the AHRQ National Guideline Clearinghouse 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.
A summary of potentially relevant trials are available in **Appendix 2**.

New Systematic Reviews:

1. A 2013 Cochrane Collaboration systematic review evaluated topical treatments for chronic plaque psoriasis[1,2] The review included 177 RCTs (n=34,808). Results demonstrated that most treatments were more effective than placebo, including vitamin-D analogues and topical corticosteroids. Potent topical corticosteroids were similarly effective; however, betamethasone twice daily was significantly more effective than betamethasone once daily. Very potent steroids had a great overall effect than potent steroids. The only very potent steroids evaluated were clobetasol and halobetasol and they resulted in similar results. Combination therapy with a vitamin D analogue plus corticosteroid was more effective than either individual product used as monotherapy. Overall, there was no statistically significant difference between vitamin D analogues and potent corticosteroids for psoriasis of the body, but corticosteroids appear more effective for treating psoriasis of the scalp. [1,2] The authors concluded that corticosteroids perform at least as well as vitamin D analogues and they are associated with a lower incidence of local adverse events.

2. A good quality systematic review by Hendriks, et al. also reviewed the efficacy and safety of first-line topical treatments for chronic plaque psoriasis.[3] A total of 45 studies were included in the analysis. Overall, the combination of steroids and vitamin D analogues were found to be more effective than either as monotherapy. There was no significant difference between the combination of clobetasol with either calcipotriene ointment or calcitriol. Another systematic review confirmed that the combination of vitamin D analogues plus topical steroids is more effective than vitamin D analogues alone. [4]

3. A systematic review evaluated the treatment of palmoplantar pustular psoriasis, which is a variant of psoriasis associated with psoriatic arthritis. [7] Twenty nine articles were included and the main outcomes were improvement in more than 70% of initial disease severity and clearance of disease. Topical corticosteroids appeared to relieve symptoms; no therapy was proven to suppress the disease completely. Based on the limited evidence, the overall recommendations were mostly based on expert opinion. It was recommended that first line therapy include potent or very potent topical corticosteroids.

4. A 2014 Cochrane Collaboration systematic review compared the effectiveness of topical corticosteroids for treating phismosis in boys.[5] A total of 12 studies (n=1395) found low quality evidence that compared with placebo, topical corticosteroids significantly increased complete or partial clinical resolution of phimosis (RR 2.45; 95% CI 1.84 to 3.26). However, due to inadequate reporting it was difficult to assess the quality of the clinical trials. Topical corticosteroids remain a first line option before surgery to correct phismosis in boys. There was no difference or preference between topical corticosteroids included in the analysis.

5. Topical corticosteroids as adjunctive therapy for bacterial keratitis were evaluated in a 2014 Cochrane Collaboration systematic review.[6] Only four RCTs met inclusion criteria for the review (n=611). None of the trials found any difference between corticosteroids and placebo in visual acuity. The authors concluded that there is inadequate evidence to support the use of topical corticosteroids for the treatment of bacterial keratitis.

New Guidelines:
Guidelines for the management of atopic dermatitis in pediatric and adults with topical therapies were published in 2014 by the American Academy of Dermatology.[7] Recommendations for the use of topical corticosteroids are provided as followed:

- Topical corticosteroids are recommended for individuals who have failed to respond to good skin care and regular use of emollients alone (Strength of recommendation: A; Level of evidence I).
- Patient age, areas of body patient preference and cost of medication should be considered when choosing a particular agent.
- Twice-daily application is generally recommended.
- No specific monitoring for systemic side effects is routinely recommended.
- Intermittent use of topical corticosteroids as maintenance therapy (1-2x week) on areas that commonly flare is recommended to help prevent relapses.

New FDA Drug Approvals: None identified.

New FDA Safety Alerts: None identified.

References:

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3. Hendriks AGM, Keijsers RRMC, de Jong EMGJ, Seyger MMB, van de Kerkhof PCM. Efficacy and safety of combinations of first-line topical treatments in chronic plaque psoriasis: a systematic literature review. *J Eur Acad Dermatol Venereol*. 2013;27(8):931-951. doi:10.1111/jdv.12058.

4. Devaux S, Castela A, Archier E, et al. Topical vitamin D analogues alone or in association with topical steroids for psoriasis: a systematic review. *J Eur Acad Dermatol Venereol*. 2012;26 Suppl 3:52-60. doi:10.1111/j.1468-3083.2012.04524.x.

5. Moreno G, Corbalán J, Peñaloza B, Pantoja T. Topical corticosteroids for treating phimosis in boys. In: *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd; 1996. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008973.pub2/abstract. Accessed February 20, 2015.

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7. Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol*. 2014;71(1):116-132. doi:10.1016/j.jaad.2014.03.023.

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9. Camplone G, D'Agostino M, De Simone C, et al. Efficacy and maintenance strategies of two-compound formulation calcipotriol and betamethasone dipropionate gel (Xamiol gel) in the treatment of scalp psoriasis: results from a study in 885 patients. *Journal of Dermatological Treatment*. 2014;25(1):30-33. doi:10.3109/09546634.2013.800182.

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Appendix 1: Current Status on Preferred Drug List

- Preferred Agents: ALCOMETASONE CREAM/OINTMENT, BETAMETHASONE CREAM/LOTION/OINTMENT (ALPHATREX), CLOBETASOL CREAM/OINTMENT, DESONIDE CREAM/OINTMENT, FLUOCINOLONE CREAM/SOLUTION, FLUOCINOLONE ACETONIDE, HYDROCORTISONE CREAM/OINTMENT/SOLUTION, TRIAMCINOLONE CREAM/OINTMENT
- Non Preferred Drugs: AMCINOMIDE CREAM/OINTMENT/LOTION, BETAMETHASONE/PROPYLENE GLYCOL, CLOCORTOLONE (Cloderm), DESOXIMETASONE , DIFLORASONE DIACETATE (APEXICON E) FLURANDRENOLIDE (CORDAN),), halcinomide (HALOG), HALOBETASOL, MOMETASONE, HYDROCORTISONE/ALOE/VIT E/A & D (ANTI-ITCH CREAM), PREDNICARBATE (DERMATOP), TRIAMCINOLONE/UREA/HYDROCORTISONE OINTMENT (AQUAPHILIC)

Relative Potencies of Topical Corticosteroids

Class	Drug	Dosage form(s)	Strength (%)
I. Very high potency	Augmented betamethasone dipropionate	Ointment	0.05
	Clobetasol propionate	Cream, foam, ointment	0.05
	Diflorasone diacetate	Ointment	0.05
	Halobetasol propionate	Cream, ointment	0.05
II. High potency	Amcinonide	Cream, lotion, ointment	0.1
	Augmented betamethasone dipropionate	Cream	0.05
	Betamethasone dipropionate	Cream, foam, ointment, solution	0.05
	Desoximetasone	Cream, ointment	0.25
	Desoximetasone	Gel	0.05
	Diflorasone diacetate	Cream	0.05
	Fluocinonide	Cream, gel, ointment, solution	0.05
	Halcinonide	Cream, ointment	0.1
	Mometasone furoate	Ointment	0.1
	Triamcinolone acetonide	Cream, ointment	0.5
III-IV. Medium potency	Betamethasone valerate	Cream, foam, lotion, ointment	0.1
	Clocortolone pivalate	Cream	0.1
	Desoximetasone	Cream	0.05
	Fluocinolone acetonide	Cream, ointment	0.025
	Flurandrenolide	Cream, ointment	0.05
	Fluticasone propionate	Cream	0.05
	Fluticasone propionate	Ointment	0.005
	Mometasone furoate	Cream	0.1
	Triamcinolone acetonide	Cream, ointment	0.1
V. Lower-medium potency	Hydrocortisone butyrate	Cream, ointment, solution	0.1
	Hydrocortisone probutate	Cream	0.1
	Hydrocortisone valerate	Cream, ointment	0.2
	Prednicarbate	Cream	0.1
VI. Low potency	Alclometasone dipropionate	Cream, ointment	0.05
	Desonide	Cream, gel, foam, ointment	0.05
	Fluocinolone acetonide	Cream, solution	0.01
VII. Lowest potency	Dexamethasone	Cream	0.1
	Hydrocortisone	Cream, lotion, ointment, solution	0.25, 0.5, 1
	Hydrocortisone acetate	Cream, ointment	0.5–1

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Appendix 2: New Clinical Trials

Twenty-three potentially relevant clinical trials were evaluated from the literature search. After further review, all trials were placebo controlled or non-randomized trials and were therefore excluded.

Appendix 3: Medline Search Strategy

1 topical corticosteroid.mp.914
2 aclometasone.mp.3
3 Betamethasone/ or Administration, Topical/ 21212
4 Betamethasone/ and Administration, Topical/ 234
5 Clobetasol/ 704
6 Fluocinolone Acetonide/ 310
7Hydrocortisone/ or hydrocortisone cream.mp. 24006
8 Triamcinolone Acetonide/2672
9 Betamethasone 2082
10 Fluocortolone/ or clocortolone.mp. 44
11 diflorasone.mp. 16
12 flurandrenolide.mp. or Flurandrenolone 9
13 halobetasol.mp. 25
14 prednicarbate.mp. 73
15 topical corticosteroids.mp. 1932
16 psoriasis.mp. or Psoriasis 17033
17 Dermatitis, Allergic Contact/ or Dermatitis/ or Dermatitis, Contact/ or Dermatitis, Atopic 23038
18 1 or 2 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 31810
16 or 17 38981
20 18 and 19 1409
21 limit 20 to (english language and humans and yr="2013 -Current" and (controlled clinical trial or meta analysis or randomized controlled trial or systematic reviews)) 23

7

Drug Use Research & Management Program
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Drug Use Evaluation: Drugs for Fibromyalgia

Drugs Included: See Appendix 1.

Reason for Review:
A 2010 DUE of serotonin norepinephrine receptor inhibitor (SNRI) use found duloxetine was associated with 62% of SNRI drug costs and 22% of duloxetine patients were associated with a medical claim with a fibromyalgia ICD9 code. The goal of this DUE is to summarize current evidence for fibromyalgia drug therapies, quantify the drugs used and their cost to inform policy options.

Key Questions:
1) What are current recommendations for drug treatments for fibromyalgia?
2) Are there differences in efficacy or effectiveness of drug treatments for fibromyalgia?
3) Are there differences in harms of drug treatments for fibromyalgia?
4) Are there specific populations where specific drug treatments may be more effective or safe?
5) What diagnoses are associated with patients using these drugs in the Oregon Health Plan population?

Conclusions:
- Fibromyalgia (ICD9 729.1x – 729.2x) falls at Line 621 on the Oregon Health Plan (OHP) prioritized list and treatment is not currently funded.[1]
- Limited treatment guidelines are available and in conflict with the evidence.
- Current evidence is limited to placebo-controlled trials of about 3 months' duration studying middle-aged, white females, with duloxetine being the most studied drug. Low quality evidence suggests duloxetine, milnacipran and pregabalin, the only drugs approved by the U.S. Food and Drug Administration (FDA) for fibromyalgia, in addition to amitriptyline, may be effective at reducing pain symptoms and sleep disturbances associated with fibromyalgia at the expense of increased adverse effects. Overall treatment effects are small.
- There is low quality evidence that no differences exist between these drugs on overall treatment withdrawal.
- There is insufficient evidence to determine if there are differences in efficacy or safety of drug treatments for fibromyalgia in specific subgroups (e.g., age, sex, race, co-morbid conditions) with the exception of duloxetine, for which there is low quality evidence that it is also effective in fibromyalgia patients in these specific subgroups: concomitant major depressive disorder, aged 65 years and older, non-whites, and males.
- There is significant use for non-funded pain conditions (10% of patients) and cost (>$25 million annually) of duloxetine in the OHP population. Chronic pain syndrome, low back pain and fibromyalgia are the most prevalent non-funded conditions associated with this group of drugs.

Recommendations:
- Create comprehensive drug use criteria for high cost drugs used for fibromyalgia, chronic low back pain and chronic pain syndrome.
- Continue to require prior authorization for pregabalin and milnacipran using the new comprehensive criteria and retire the current criteria for each.
- Recommend prior authorization for duloxetine using the new comprehensive criteria; grandfather current patients and apply policy to new starts.
- Allow automatic approval for prior claims and evidence of major depression for duloxetine and epilepsy for pregabalin.

Background:
Fibromyalgia is a chronic functional illness marked by widespread musculoskeletal pain often associated with other symptoms such as fatigue, sleep difficulties, cognitive dysfunction and depressed mood or depressive episodes.[2] The controversy surrounding fibromyalgia stems from the subjective nature of its complaints and lack of any defining abnormal biological findings at presentation. Women are disproportionately affected, especially in middle age.[2] Epidemiological data are limited in the United States, but the prevalence of fibromyalgia as assessed in Olmsted County, Minnesota, is 1.1% using medical records with a documented diagnosis.[3] It is unknown what may cause fibromyalgia, but proposed pathogenesis may be related to abnormal pain processing in the peripheral, central and sympathetic nervous systems and abnormal processing in the hypothalamic-pituitary-adrenal stress response axis.[2] Risk factors associated with increased risk of fibromyalgia include history of physical trauma or injury, infection (e.g., hepatitis C), stress, female sex, or having a relative with fibromyalgia.[2] Fibromyalgia is also significantly associated with a history of physical or sexual abuse, either in childhood or adulthood.[4] Patients with fibromyalgia may have substantial overlap across functional somatic syndromes such as irritable bowel syndrome, chronic pelvic pain, or chronic fatigue syndrome.[2] Patients may also have concomitant psychiatric disorders such as generalized anxiety disorder, depression, bipolar disorder or posttraumatic stress disorder.[2] Associated autoimmune disorders such as systemic lupus erythematosus (SLE), rheumatoid arthritis or ankylosing spondylitis are also reported.[2] Not surprisingly, fibromyalgia reduces quality of life and is associated with functional disability, lost work time, and increased use of health care services.[5]

Treatments for fibromyalgia include drugs and non-pharmacologic therapies with goals including mitigating diffuse musculoskeletal pain, maximizing physical and cognitive function, optimizing patient self-management and managing comorbid medical and psychiatric disorders. The FDA has approved three oral medications for fibromyalgia since 2007: pregabalin, duloxetine and milnacipran. Several drugs have also been used off-label for fibromyalgia, including antidepressants, NSAIDs, opioid analgesics, and skeletal muscle relaxants.[5]

Fibromyalgia (ICD9 729.1x – 729.2x) falls at Line 621 on the Oregon Health Plan (OHP) prioritized list and treatment is not currently funded.[1] Pregabalin (April 2008) and milnacipran (January 2010) both require prior authorization to confirm use for a funded OHP condition. Duloxetine, a serotonin norepinephrine receptor inhibitor (SNRI), currently has no restriction for diagnosis and is carved-out of coordinated care plan contracts. Duloxetine is also FDA-indicated for major depressive disorder and diabetic peripheral neuropathy (Appendix 1).

Systematic Reviews:
The Drug Effectiveness Review Project (DERP) Report[6]
The Drug Effectiveness Review Project (DERP) conducted a systematic review on the evidence for comparative effectiveness/efficacy and comparative harms of the drugs used to treat fibromyalgia. Differences in any subgroups of patients based on demographics, socioeconomic status, other medications, or comorbidities for which any included drugs were more effective or associated with less harm were also assessed.[6] Drugs identified in eligible studies included:

Tricyclic Antidepressants (TCAs)
- Amitriptyline
- Nortriptyline

Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)
- Duloxetine
- Milnacipran

Skeletal Muscle Relaxants
- Cyclobenzaprine

Selective Serotonin Reuptake Inhibitors (SSRIs)
- Citalopram
- Fluoxetine
- Paroxetine

Antiepileptics, Misc.
- Gabapentin
- Pregabalin

Head-to-head evidence is sparse and low quality. Amitriptyline, pregabalin, milnacipran and duloxetine are the only drugs with sufficient number of placebo-controlled trials homogeneous enough to combine their results. These drugs are nearly always studied as monotherapy. There was no significant difference between pregabalin, milnacipran and duloxetine on response rate of 30% or 50% improvement in pain. There is no difference between amitriptyline, pregabalin, milnacipran and duloxetine on function as measured by the Fibromyalgia Impact Questionnaire (FIQ) and there is no difference between duloxetine, milnacipran, or pregabalin on the physical or mental components of the Medical Outcomes Study 36-item Short-Form Health Survey. Amitriptyline is the only drug that has sufficient evidence to report on measures of pain at 28 weeks.[6]

A recent DERP update of this review in November 2014 did not identify any new head-to-head trials for treatment of fibromyalgia. Placebo-controlled studies and post-hoc analyses continue to show relative improvement in pain and sleep disturbance symptoms for higher doses of duloxetine (60 to 120 mg daily), milnacipran (as monotherapy or adjunctive therapy to pregabalin), pregabalin, mirtazapine, and low-dose cyclobenzaprine.[7] Placebo-controlled studies show gabapentin significantly improves pain severity and response, overall impact of fibromyalgia, global status, and sleep compared to placebo, but not tender point pain threshold, depression or overall quality of life. Fluoxetine is the only SSRI, at a higher dose of 45 mg daily, that significantly improves pain, fatigue and FIQ scores compared to placebo. Paroxetine improves FIQ scores, fatigue and global status, but not pain, disability, or interestingly, not depression. Citalopram also has mixed results. Cyclobenzaprine only significantly reduced pain relative to placebo in 1 of 3 trials.[6]

There is low quality evidence that no differences exist between these drugs on overall treatment withdrawal. Overall adverse effects, especially anticholinergic-type effects, are more frequent with amitriptyline than paroxetine; and nortriptyline is associated with more overall adverse effects than amitriptyline. There are no differences between cyclobenzaprine and amitriptyline in any harms outcomes. When indirectly comparing drugs based on placebo-controlled trials, all drugs are generally well tolerated with greater adverse events (e.g., dizziness, sedation, lightheadedness, and weight gain) reported compared to placebo; pregabalin has significantly less headache, nausea and diarrhea compared to duloxetine, and significantly less headache and nausea compared to milnacipran. There are no differences between duloxetine and milnacipran in incidence of hyperhidrosis, though rates are significantly higher for both compared to placebo. Milnaciprain has significantly more tachycardia than placebo (number needed to harm 21; 95% CI, 16 to 30) and pregabalin has significantly more weight gain (relative risk, 4.58; 95% CI, 2.44 to 6.82) and peripheral edema (relative risk, 3.52; 95% CI, 2.01 to 6.18) relative to placebo. There is insufficient evidence on harms reported in placebo-controlled trials of the other drugs.[6]

There is extremely limited evidence regarding treatment of fibromyalgia in specific subgroup populations. The majority of patients in trials are middle-aged, white (84% to 91%) females (89% to 100%). Duloxetine is an exception and has been studied in different subgroups; it is no different than placebo in pain response in male patients, those 65 years of age and older, and non-white patients.[6]

The Agency for Healthcare Research and Quality (AHRQ) Report

The Agency for Healthcare Research and Quality (AHRQ) recently performed a systematic comparative effectiveness review through one of its Evidence-based Practice Centers for treatments of fibromyalgia in adult subgroups. The subgroups of interest included women, older or obese adults, individuals with coexisting mental health conditions, high severity or longer fibromyalgia duration, multiple medical comorbidities, or other chronic pain conditions. Primary outcomes included pain, symptom improvement, function, fatigue, sleep quality, participation, and health-related quality of life. Only 22 randomized controlled trials (RCTs), 8 pooled analyses of patient-level RCT data, and 4 observational studies met inclusion criteria; and only 59% were drug trials.[5]

Overall, evidence is largely insufficient to determine the effects of treatments on the subgroups studied other than duloxetine in adults with fibromyalgia. Study patients are largely middle-aged white females with moderate to severe fibromyalgia symptoms at baseline as measured by the FIQ, which is generally representative of the fibromyalgia population seen in clinical practice in the U.S. Most drug trials are placebo-controlled RCTs. Other comparators include standard care; standard care plus adjunctive therapy; normal activities; or education and information sessions. All but two individual RCTs have high risk of bias, primary due to high attrition (30-40%), and studies are overwhelmingly short-term (3 months) for a chronic, long-term condition. A meta-analysis was not conducted given the sparse evidence for specific treatments and outcomes of these subgroups.[5]

Duloxetine is the most studied drug (9 studies) and the most studied subgroup is in patients with major depressive disorder (MDD) (12 studies), followed by age (7 studies), sex (6 studies), anxiety (4 studies), obesity/body mass index (2 studies), and medical comorbidities (1 study). Less information is available on other subgroups. Outcomes other than pain, as well as non-pharmacologic interventions, are also very limited. Overall, limited, low quality evidence suggests duloxetine does not have any differential effect on pain or depression (Hamilton Depression Scale) in adults with fibromyalgia and MDD versus fibromyalgia patients without MDD. Sparse, low quality evidence suggests that the effects of duloxetine on global improvement (PGI-I) scores and FIQ scores also do not differ. Evidence is insufficient regarding the effects of milnacipran on Visual Analog Scale pain scores in adults with fibromyalgia and MDD versus the general fibromyalgia population. Limited, low quality RCT evidence for the effects of duloxetine by age (on BPI average pain and PGI-I), sex (on PGI-I) and race (on PGI-I) suggest that treatment effects do not differ in these subgroups versus the general fibromyalgia population. In general, overall treatment effects are small, and even less so when substantial placebo-group improvements are considered relative to the treatment effects. Subgroup effects parallel the magnitude and direction of overall treatment and placebo effects in mixed-sample studies. The effect of attrition within subgroups was missing so the extent to which studies could detect a difference even if one existed could not be determined, particularly since power calculations, when reported, were conducted to detect main group effects, not subgroup effects. Data are insufficient for the other treatments, including pregabalin and milnacipran, to evaluate their effects on any specific subgroups.[5]

Extensive exclusion criteria in these studies likely contribute to the lack of data in these subgroups. The fibromyalgia evidence is largely insufficient to determine subgroup effects for drug treatments other than duloxetine in patients with MDD. Unfortunately, patients with fibromyalgia and multi-morbid conditions are a clinical reality. Thus, the limitations of the primary literature preclude any change of policy or practice based on these findings.[5]

Guidelines:

Evidence-based guidelines for the management of fibromyalgia are primarily limited to the *Canadian Guidelines for the Diagnosis and Management of Fibromyalgia Syndrome in Adults*,[8] which is endorsed by the Canadian Pain Society and the Canadian Rheumatology Association. Some of the recommendations presented in the guideline conflict with the systematic reviews presented here.

The grading system for its recommendations is based on guidance provided by the Oxford Centre for Evidence-based Medicine and consists of levels of evidence and grades of recommendation[8]:

- Level 1 - systematic review of randomized trials
- Level 2 - randomized trial or (exceptional) observational study with dramatic effect
- Level 3 - nonrandomized controlled cohort/follow-up study
- Level 4 - systematic review of case-control studies or historically controlled studies
- Level 5 - opinion

- Grade A - consistent Level 1 studies
- Grade B - consistent Level 2 or Level 3 studies, or extrapolations from Level 1 studies
- Grade C - Level 4 studies or extrapolations from Level 2 or Level 3 studies
- Grade D - Level 5 evidence or concerning, inconsistent or inconclusive studies of any level
- Consensus - opinion

Though studies commonly evaluate drugs like duloxetine and milnacipran as monotherapy, this guideline recommends choice of drug therapy be guided by symptoms, which may require combination of medications (Level 1, Grade A).[8]

Tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) may be used to treat pain and other symptoms, such as fatigue and depression, in patients with fibromyalgia (Level 1, Grade A).[7] The guideline does not provide detailed recommendations regarding specific antidepressants, dosing and step therapy, but the following antidepressants have been most studied[2,8]:

- Amitriptyline 25-50 mg nightly (TCA)
- Cyclobenzaprine 10-30 mg nightly (TCA properties)
- Duloxetine 60 mg daily (SNRI)
- Milnacipran 50 mg twice daily (SNRI)
- Paroxetine and fluoxetine (SSRIs)

Analgesics such as acetaminophen may be useful at safe doses (Level 5, Consensus). NSAIDs should only be prescribed at the lowest dose for the shortest time period possible to avoid adverse effects (Level 5, Grade D). Opioid therapy should be reserved for patients with moderate-to-severe pain that is unresponsive to other treatments; but treatment should be started with a weak opioid such as tramadol (Level 2, Grade D).[8] Lastly, antiepileptic drugs may be effective for their pain-modulating properties; both pregabalin and gabapentin may reduce pain and other symptoms of fibromyalgia (Level 1, Grade A).[8]

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Methods:
A cross-section of patients with a paid fee-for-service (FFS) or encounter paid drug claim in calendar year 2014 for any drug in Appendix 1 were included. Patients with Medicare Part D coverage as identified with benefit package BMM or BMD were excluded. The study population was those with $\geq$ 75% days of eligibility of 365 days prior to index claim for a drug of interest. The comparison group was the total population without the eligibility exclusion. Patients were flagged for diagnoses of interest in Appendix 2 if there was a paid FFS or encounter claim with the diagnosis code from 1 year prior to index drug claim through 2014.

Results:
Table 1 displays the demographics of the patients on fibromyalgia drugs. The majority of patients on the drugs of interest were female (66-70%), 26-64 years old (85-89%) and Caucasian (78-80%).

Table 1 - Demographics

	Total		Study	
N=	87,572	%	51,434	%
Female	57,915	66.1%	35,740	69.5%
Mean age (range)	41.9	(1-92)	40.9	(1-92)
<= 12	488	0.6%	439	0.9%
13-25	9,981	11.4%	7,192	14.0%
26-65	76,877	87.8%	43,612	84.8%
>65	226	0.3%	191	0.4%
Caucasian	68,045	77.7%	41,305	80.3%

Over $25 million was paid to pharmacies for these drugs in 2014 for all OHP patients. Using an assumed 30% rebate rate, the net cost is estimated to be $17.5 million annually. Table 2 reveals duloxetine is associated with more than 60% of pharmacy reimbursed drug costs within this group of drugs while only 10% of patients (Table 3). Gabapentin is associated with 10% of drug costs and 23% of patients, whereas pregabalin is associated with 9% of costs and just 1% of patients. There is almost no use of milnacipran.

Table 4 categorizes patients as those who have only non-funded conditions (fibromyalgia, low back pain or chronic pain syndromes), those that have a funded condition (e.g. major depression, anxiety or neuropathy) or those with none of the selected diagnoses in Appendix 2 for each drug. Those with both a funded and non-funded condition were placed in the funded group. Drugs with the highest rates of only non-funded conditions were the tricyclic antidepressants (7.6% - 36.7%), gabapentin (20.6%), pregabalin (11.4%) and duloxetine (10.6%). Chronic pain syndrome or chronic back pain is the most prevalent non-funded conditions for all drugs.

Table 2 – Total Fibromyalgia Drug Utilization and Cost (Amount Paid on Claim) CY 2014

			Total Patients				Study Patients			
Class Group	**HSN**	**Generic Name**	**Sum Claim Count**	**Sum Claim Cost**	**Market Share by Cost**	**Mean Cost / claim**	**Sum Claim Count**	**Sum Claim Cost**	**Market Share by Cost**	**Mean Cost / claim**
AED	08831	gabapentin	137,154	$2,541,765	10%	$19	85,037	$1,675,950	10%	$20
AED	26470	pregabalin	7,525	$2,185,954	8%	$290	5,358	$1,562,327	9%	$292
SNRI 1	08847	venlafaxine HCl	60,287	$1,970,282	8%	$33	34,470	$1,184,855	7%	$34
SNRI 1	21229	milnacipran HCl	49	$7,895	0%	$161	19	$3,091	0%	$163
SNRI 1	26521	duloxetine HCl	75,559	$15,884,328	61%	$210	49,042	$10,663,069	62%	$217
SNRI 2	35420	desvenlafaxine succinate	5,764	$1,255,337	5%	$218	3,873	$859,118	5%	$222
SNRI 2	40202	desvenlafaxine	260	$43,813	0%	$169	114	$20,641	0%	$181
SNRI 2	40632	levomilnacipran HCl	1,067	$239,801	1%	$225	652	$143,810	1%	$221
SNRI 2	40692	desvenlafaxine fumarate	6	$876	0%	$146	6	$876	0%	$146
TCA	01641	imipramine HCl	3,712	$65,807	0%	$18	2,805	$49,166	0%	$18
TCA	01642	imipramine pamoate	184	$57,246	0%	$311	134	$40,760	0%	$304
TCA	01643	amitryptyline HCl	64,850	$793,822	3%	$12	40,904	$519,244	3%	$13
TCA	01644	nortriptyline HCl	19,440	$234,162	1%	$12	11,498	$141,253	1%	$12
TCA	01645	desipramine HCl	779	$59,606	0%	$77	566	$45,690	0%	$81
TCA	01950	cyclobenzaprine HCl	114,626	$490,204	2%	$4	69,048	$299,722	2%	$4
		Totals	491,262	$25,830,898			303,526	$17,209,571		

AED = Alpha2-ligand Anti-Epileptic Drugs; SNRI-1 = 1st generation Serotonin Norepinephrine Receptor Inhibitor; SNRI-2 = 2nd generation Serotonin Norepinephrine Receptor Inhibitor; TCA = Tri-Cyclic Antidepressants

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Table 3 - Index Drug Patient Distribution

Class Group	HSN	Generic Name	N=	Total 87,572	%	Study 51,434	%
AED	00883	gabapentin		20,750	23.7%	11,961	23.3%
AED	02647	pregabalin		655	0.7%	472	0.9%
SNRI 1	00884	venlafaxine HCl		7,997	9.1%	4,387	8.5%
SNRI 1	02122	milnacipran HCl		4	0.0%	1	0.0%
SNRI 1	02652	duloxetine HCl		8,677	9.9%	5,404	10.5%
SNRI 2	03542	desvenlafaxine succinate		744	0.8%	480	0.9%
SNRI 2	04020	desvenlafaxine		35	0.0%	13	0.0%
SNRI 2	04063	levomilnacipran HCl		163	0.2%	98	0.2%
SNRI 2	04069	desvenlafaxine fumarate		1	0.0%	1	0.0%
TCA	00164	amitryptyline HCl		10,229	11.7%	6,256	12.2%
TCA	00164	desipramine HCl		151	0.2%	105	0.2%
TCA	00164	imipramine HCl		593	0.7%	436	0.8%
TCA	00164	imipramine pamoate		20	0.0%	14	0.0%
TCA	00164	nortriptyline HCl		3,320	3.8%	1,956	3.8%
TCA	00195	cyclobenzaprine HCl		34,233	39.1%	19,850	38.6%

AED = Alpha2-ligand Anti-Epileptic Drugs; SNRI-1 = 1st generation Serotonin Norepinephrine Receptor Inhibitor; SNRI-2 = 2nd generation Serotonin Norepinephrine Receptor Inhibitor; TCA = Tri-Cyclic Antidepressants

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Table 4 – Diagnosis Distribution by Index Drug - Study Group Only

AED Drugs	gabapentin		pregabalin	
N=	11,961	%	472	%
#1) Only Not-Funded - FIBROMYALGIA	133	1.1%	7	1.5%
#2) Only Not-Funded – BACK / CHRONIC PAIN	1,864	15.6%	24	5.1%
Only Group #1 & #2 present	463	3.9%	23	4.9%
Total patients with only non-funded diagnosis present	14,421	20.6%	526	11.4%
Patients with selected funded diagnosis present	8,298	69.4%	399	84.5%
No selected diagnosis present	1,203	10.1%	19	4.0%

SNRI 1 Drugs	duloxetine		milnacipran		venlafaxine	
N=	5,404	%	1	%	4,387	%
#1) Only Not-Funded - FIBROMYALGIA	59	1.1%		0.0%	15	0.3%
#2) Only Not-Funded – BACK / CHRONIC PAIN	350	6.5%		0.0%	191	4.4%
Only Group #1 & #2 present	163	3.0%		0.0%	38	0.9%
Total patients with only non-funded diagnosis present	572	10.6%	0	0.0%	244	5.6%
Patients with selected funded diagnosis present	4,500	83.3%	1	100.0%	3,747	85.4%
No selected diagnosis present	332	6.1%		0.0%	396	9.0%

SNRI 2 Drugs	desvenlafaxine		des. fumarate		des. succinate		levomilnacipran	
N=	13	%	1	%	480	%	98	%
#1) Only Not-Funded - FIBROMYALGIA		0.0%		0.0%		0.0%		0.0%
#2) Only Not-Funded – BACK / CHRONIC PAIN	1	7.7%		0.0%	17	3.5%	3	3.1%
Only Group #1 & #2 present		0.0%		0.0%	3	0.6%	1	1.0%
Total patients with only non-funded diagnosis present	1	7.7%	0	0.0%	20	4.2%	4	4.1%
Patients with selected funded diagnosis present	11	84.6%	1	100.0%	422	87.9%	89	90.8%
No selected diagnosis present	1	7.7%		0.0%	38	7.9%	5	5.1%

TCA Drugs	amitryptyline		cyclobenzaprine		desipramine		imipramine		imipramine pamoate		nortriptyline	
N=	6,256	%	19,850	%	105	%	436	%	14	%	1,956	%
#1) Only Not-Funded - FIBROMYALGIA	72	1.2%	151	0.8%	1	1.0%	2	0.5%		0.0%	29	1.5%
#2) Only Not-Funded – BACK / CHRONIC PAIN	873	14.0%	6,497	32.7%	15	14.3%	24	5.5%		0.0%	274	14.0%
Only Group #1 & #2 present	198	3.2%	631	3.2%		0.0%	7	1.6%	1	7.1%	75	3.8%
Total patients with only non-funded diagnosis present	1,143	18.3%	7,279	36.7%	16	15.2%	33	7.6%	1	7.1%	378	19.3%
Patients with selected funded diagnosis present	4,002	64.0%	9,700	48.9%	70	66.7%	262	60.1%	10	71.4%	1,183	60.5%
No selected diagnosis present	1,111	17.8%	2,871	14.5%	19	18.1%	141	32.3%	3	21.4%	395	20.2%

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Appendix 1 – Drugs indicated for fibromyalgia

Therapeutic Class	HSN	Generic Name	Major Depressive Disorder	Seizure	Fibromyalgia	Peripheral Herpetic Neuropathy	Diabetic Peripheral Neuropathy	Other Peripheral Neuropathy
Tricyclic Antidepressants	001643	amitryptyline HCl	x		?	?		?
Tricyclic Antidepressants	001950	cyclobenzaprine HCl			?			
Tricyclic Antidepressants	001645	desipramine HCl	x		?			
Tricyclic Antidepressants	001641	imipramine HCl	x				?	
Tricyclic Antidepressants	001642	imipramine pamoate	x				?	
Tricyclic Antidepressants	001644	nortriptyline HCl	x			?		
SNRI-1 Antidepressants	026521	duloxetine HCl	x		x		x	?
SNRI-1 Antidepressants	021229	milnacipran HCl	?		x			
SNRI-1 Antidepressants	008847	venlafaxine HCl	x		?			
SNRI-2 Antidepressants	040202	desvenlafaxine	x					
SNRI-2 Antidepressants	040692	desvenlafaxine fumarate	x					
SNRI-2 Antidepressants	035420	desvenlafaxine succinate	x					
SNRI-2 Antidepressants	040632	levomilnacipran HCl	x					
Alpha2-ligand AED	008831	gabapentin		x	?		?	
Alpha2-ligand AED	026470	pregabalin		x	x	x	x	x

X = FDA indication ?=reported off-label use in Micromedex 2.0, Dynamed or UpToDate

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Appendix 2 – Diagnoses of Interest

Not-Funded Diagnosis Group #1	ICD9
DISORDERS OF SOFT TISSUE	
Myalgia and myositis, unspecified	7291x
Neuralgia, neuritis, and radiculitis, unspecified	7292x
Not-Funded Diagnosis Group #2	ICD9
ACUTE AND CHRONIC DISORDERS OF SPINE WITHOUT NEUROLOGIC IMPAIRMENT	
Syringomyelia and syringobulbia	3360x
Disorders of meninges, not elsewhere classified	3492x
Sacroiliitis, not elsewhere classified	7202x
Inflammatory spondylopathies in diseases classified elsewhere	72081
Cervical spondylosis without myelopathy	7210x
Thoracic spondylosis without myelopathy	7212x
Lumbosacral spondylosis without myelopath	7213x
Traumatic spondylopathy	7217x
Other allied disorders of spine	7218x
Spondylosis of unspecified site, without mention of myelopathy	72190
Intervertebral disc disorders	722xx
Cervicalgia	7231x
Brachial neuritis or radiculitis NOS	7234x
Other disorders of cervical region	7236x - 7239x
Pain in thoracic spine/Lumbago	7241x-7242x
Backache, unspecified	7244x-7249x
Nonallopathic lesions not elsewhere classified	739xx
Other specified congenital anomalies of spinal cord	74259
Congenital musculoskeletal deformities of sternocleidomastoid muscle	7541x
Closed dislocation thoracic and lumbar vertebra	8392x
Sprains and strains of other and unspecified parts of back	847xx
CHRONIC PAIN (EXCLUDED DIAGNOSES)	
Chronic pain d/t trauma	33820-33821
Other chronic pain	33829
Chronic pain syndrome	3384x

Funded Diagnosis Group #3	ICD9
Hereditary and idiopathic peripheral neuropathy	356xx
Diabetes with neurological manifestations	2506x
Herpes zoster with nervous system complications	0531x
MDD or Depressive disorder, NOS	311xx
Major Depressive Disorder	2962x; 2963x
Anxiety disorders	300xx
Epilepsy and recurrent seizures	345xx

Appendix 3 Proposed new PA criteria

Drugs Used for Non-Funded Pain Conditions

Goal(s):

- Provide coverage only for funded diagnoses that are supported by the medical literature (e.g. major depressive disorder, epilepsy, diabetic neuropathy, post-herpetic neuralgia).

Length of Authorization:

90 days to lifetime (criteria specific)

Requires PA:

- duloxetine, milnacipran, pregablin

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is the drug requested pregablin AND does client have a diagnosis of epilepsy? (ICD-9 code 345.0-345.9, 780.39, or 907.0)	Yes: Approve for lifetime (until 12-31-2036)	No: Go to #3.
3. Is the drug requested duloxetine AND does the client have an anxiety disorder or depressive disorder (ICD9 296xx, 300xx, 309xx, 311xx)?	Yes: Approve for lifetime (until 12-31-2036)	No: Go to #4.
4. Is the diagnosis funded on the OHP list of prioritized services (See Table below for examples)?	Yes: Approve for 90 days to 1 year.	No: Pass to RPH; Go to #5.

Approval Criteria

5. Pass to RPH
   - For Bipolar affective disorder: there are no data to support use of any of these drugs for this indication (Deny Medical Appropriateness). Recommend other alternatives (lithium, valproate, carbamazepine, lamotrigine).
   - For Migraine prophylaxis: there are no data to support use of any of these drugs for this indication (Deny Medical Appropriateness). Recommend other alternatives (beta-blockers, calcium channel blockers, valproate, gabapentin, TCAs). Refer to American Academy of Neurology Guideline.
   - If clinically warranted, may DENY yesterday's date (Medical Appropriateness) and use clinical judgment to APPROVE for 1 month starting today to allow time for appeal.

   All other indications need to be evaluated to see if diagnosis is funded:
   - Funded neuropathies found in table (list is not all-inclusive) may be approved for 90 days with subsequent approvals dependent on documented positive response (documented response means that follow-up and response is noted in client's chart per clinic staff).
   - **Forward any neuropathy/neuralgia ICD-9 codes not found in the Table to the Lead Pharmacist. These codes will be forwarded to DMAP for consideration.**

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Table

Not-Funded Diagnoses	ICD9
DISORDERS OF SOFT TISSUE	
Myalgia and myositis, unspecified (includes fibromyalgia syndromes)	7291x
Neuralgia, neuritis, and radiculitis, unspecified	7292x
ACUTE AND CHRONIC DISORDERS OF SPINE WITHOUT NEUROLOGIC IMPAIRMENT	
Syringomyelia and syringobulbia	3360x
Disorders of meninges, not elsewhere classified	3492x
Sacroiliitis, not elsewhere classified	7202x
Inflammatory spondylopathies in diseases classified elsewhere	72081
Cervical spondylosis without myelopathy	7210x
Thoracic spondylosis without myelopathy	7212x
Lumbosacral spondylosis without myelopath	7213x
Traumatic spondylopathy	7217x
Other allied disorders of spine	7218x
Spondylosis of unspecified site, without mention of myelopathy	72190
Intervertebral disc disorders	722xx

Cervicalgia	7231x
Brachial neuritis or radiculitis NOS	7234x
Other disorders of cervical region	7236x - 7239x
Pain in thoracic spine/Lumbago	7241x-7242x
Backache, unspecified	7244x-7249x
Nonallopathic lesions not elsewhere classified	739xx
Other specified congenital anomalies of spinal cord	74259
Congenital musculoskeletal deformities of sternocleidomastoid muscle	7541x
Closed dislocation thoracic and lumbar vertebra	8392x
Sprains and strains of other and unspecified parts of back	847xx
CHRONIC PAIN (EXCLUDED DIAGNOSES)	
Chronic pain d/t trauma	33820-33821
Other chronic pain	33829
Chronic pain syndrome	3384x
Funded Diagnoses	ICD9
Hereditary and idiopathic peripheral neuropathy	356xx
Diabetes with neurological manifestations	2506x
Herpes zoster with nervous system complications	0531x

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P&T / DUR Action: *3/26/15; 5/09; 9/07; 11/07*
Revision(s): *TBD; 1/11; 1/10*
Initiated: *4/08*

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Class Update: Proton Pump Inhibitors and Histamine-2 Receptor Antagonists

Month/Year of Review: March 2015

Date of Last Review: Proton Pump Inhibitors: March 2014
Histamine-2 Receptor Antagonists: January 2013

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

Purpose for Class Update:
The Health Evidence Review Commission (HERC) is limiting the funding for treatment of gastro-esophageal reflux disease (GERD) to 8 weeks on the OHP Prioritized List of Health Services. Prior Authorization (PA) criteria are in place for non-preferred PPIs to promote PDL options. There is currently open access to preferred PPIs and H2RAs.

Research Questions:
- What is the comparative effectiveness of different proton pump inhibitors (PPIs) in patients being treated for symptoms of gastro-esophageal reflux, gastro-esophageal reflux disease (GERD), peptic (gastric or duodenal) ulcer disease (PUD) or non-steroidal anti-inflammatory drug (NSAID)-induced ulcers?
- What is the comparative effectiveness of different histamine-2 receptor antagonists (H2RAs) in patients being treated for symptoms of gastro-esophageal reflux or GERD?
- What is the comparative safety of different PPIs in patients being treated for symptoms of gastro-esophageal reflux, PUD or NSAID-induced ulcers?
- What is the comparative safety of different H2RAs in patients being treated for symptoms of gastro-esophageal reflux?
- Is there evidence that long-term treatment (>8 weeks) of GERD or symptoms of gastro-esophageal reflux with a PPI is more effective than short-term treatment (≤8 weeks)?
- Are there specific sub-populations in which a specific PPI or H2RA may be more effective or associated with increased harms?

Previous Conclusions and Recommendations:
Proton Pump Inhibitors
- Patients should be re-evaluated for benefits and risks while on long-term PPI therapy for potential adverse events.
- There is no consistent difference in efficacy or safety between PPIs to justify selection of any PPI as clinically superior to the other drugs in the class.
- No evidence supports differences in efficacy or adverse effects in subpopulations by race and ethnicity, age, gender, or co-morbidities.

Histamine 2-Receptor Antagonists
- Evidence does not support a difference in efficacy or harms.
- Cimetidine is associated with more adverse events; ranitidine has the second most adverse events.
- Consider inclusion of at least one H2RA with special consideration for famotidine or ranitidine for pediatric use.

Conclusions and Recommendations:

- There is high quality evidence that there is no difference in effectiveness between PPIs for healing and maintaining remission of erosive gastro-esophagitis based on endoscopy, relieving symptoms of heartburn for up to 8 weeks, or treatment of PUD or NSAID-induced ulcers.
- There is high quality evidence that there is no difference in efficacy between H2RAs for the management of gastro-esophageal reflux or GERD.
- There is moderate quality evidence that there are no differences in harms between different PPIs or between H2RAs. In general, long-term use of PPIs are associated with severe adverse effects that are not associated with H2RAs
    - No association between outpatient use of H2RAs and risk for *Clostridium difficile*-associated diarrhea was found; this evidence conflicts with previous evidence that suggested an association with chronic PPI use does exist.
    - Patients on long-term PPI therapy should receive an annual re-evaluation to determine need for continued therapy secondary to increased harms, including osteoporosis, *Clostridium difficile*–associated diarrhea and certain nutritional deficiencies. However, the accumulating evidence from better designed, prospective clinical studies cannot substantiate the initial concerns for adverse cardiovascular effects of PPI use in patients on clopidogrel originally seen in the retrospective cohort studies.
- There is high quality evidence that there is no difference between long-term treatment of PPIs and short-term treatment of PPIs for erosive gastro-esophagitis based on endoscopy.
- There is insufficient evidence for long-term treatment of PPIs for symptomatic GERD as most studies evaluating PPIs for the management of GERD are limited to 8 weeks' duration.
- There is insufficient evidence to suggest long-term PPI use significantly decreases incidence of esophageal adenocarcinoma and/or high-grade dysplasia in patients with Barrett's esophagus. The role of PPIs in Barrett's esophagus remains uncertain due to conflicting observational data.
- There is moderate quality evidence that there is no difference in safety or efficacy between PPIs in managing symptoms of reflux in the pediatric population aged 1 year and older. Evidence for use of H2RAs is limited to ranitidine. There is insufficient evidence for use of these agents in infants.
- Low quality evidence suggests PPIs and H2RAs in Cystic Fibrosis patients improves gastrointestinal symptoms and fat absorption but there is insufficient evidence of their effect on nutritional status, lung function, quality of life or mortality.
- Use current evidence and data presented in the PPI/H2RA Drug Use Evaluation to guide new PA criteria.
- Evaluate comparative drug costs for both classes in the executive session.

Background:

Dyspepsia describes a range of symptoms that arise from the upper gastrointestinal (GI) tract, but it has no universally accepted definition.[1] These symptoms, which typically present for 4 weeks or more, include upper abdominal pain or discomfort, heartburn, gastric reflux, nausea or vomiting.[1] Gastro-esophageal reflux can also cause a variety of gastroesophageal symptoms (i.e., heartburn and regurgitation) but can also cause extraesophageal symptoms (i.e., chronic cough, hoarseness, sore throat) and can overlap substantially with other disorders such as dyspepsia, irritable bowel syndrome, respiratory disorders or somatoform disorders.[2] Patients with GERD can also present with dysphagia, upper GI bleeding, chest pain and epigastric pain – "red flag" symptoms that should be clarified by immediate appropriate diagnostic evaluation. GERD is a multifactorial disorder related mainly to failure of the anti-reflux mechanisms. The pathophysiologic components of GERD, which can be either alone or combined, can include: a mechanically defective lower esophageal sphincter (LES); transient

LES relaxation; a hiatal hernia; insufficient esophageal peristalsis; delayed gastric emptying or impaired esophageal clearance. Several factors such as stress, obesity, pregnancy, diet or drugs can also play a role in the pathophysiology of GERD.

Epidemiologic data on GERD are not reliable largely because data are based on subjective symptoms such as heartburn and regurgitation. Using these data, prevalence ranges between 0.1% and 20% in industrial countries. The natural course of GERD is chronic but the majority of patients with GERD will remain within the initial level of severity of disease at diagnosis; about 4-7% of patients progress and develop further complications. Endoscopy is the most important diagnostic investigation to prove the presence of GERD, which can distinguish between non-erosive reflux disease (NERD) and erosive reflux disease (ERD) and Barrett's esophagus (BE).[2]

The primary goals of medical therapy for GERD are to control heartburn, heal gastroesophageal mucosal injuries and improve patient quality of life. Patients should avoid large meals and lying down within 3 hours after eating. Ingestion of fatty or spicy foods, chocolate, coffee, peppermint, citrus fruits and juices, tomato, carbonated drinks and alcohol may also increase reflux events and GERD symptoms. Weight loss also reduces risk for GERD and makes acid suppressant therapy more effective. Antacids are well tolerated, safe and effective in reducing heartburn and controlling acid regurgitation in patients with mild reflux disease. Proton pump inhibitors and H2RAs represent the mainstay of GERD medical treatment and provide healing and symptomatic relief in patients with esophageal syndromes.[2] An 8-week course of PPIs is recommended for symptomatic GERD.[3] Zollinger-Ellison syndrome and other related conditions often require longer duration of PPI therapy because of the presence refractory ulcers in the upper GI tract.[3]

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes since the last DURM review were conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. Time limits included restricting evidence published since the PPI class was last reviewed by the P&T committee in March 2014 and the H2RA class in January 2013. 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, Dynamed, 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 drugs, 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:

<u>Effectiveness of PPIs and H2RAs</u>

PPIs and H2RAs in the Adult Population

The pathogenesis of NERD and its response to treatment may differ from GERD with esophagitis. A Cochrane systematic review was performed in order to summarize, quantify and compare the efficacy of short-term use of PPIs and H2RAs in adults with GERD, treated either empirically without diagnosis by

endoscopy or in those with NERD. A total of 1,314 participants were studied in 24 double-blind, parallel group studies of one to 12 weeks' duration. Fifteen trials were eligible for inclusion in the endoscopy group, 15 trials were eligible for inclusion in the NERD group and 4 trials included both groups. Use of antacids was permitted in most of the studies. In the empiric group, the risk for heartburn remission, the primary efficacy variable studied, was significantly lower for PPIs than for the H2RAs in placebo-controlled studies (relative risk (RR) 0.37; 95% CI, 0.32 to 0.44 vs. RR 0.77; 95% CI, 0.60 to 0.99, respectively). In head-to-head studies, PPIs were also significantly more effective than H2RAs (RR 0.66; 95% CI, 0.60 to 0.73). In patients with NERD, the risk for heartburn remission was relatively equal between PPIs and H2RAs in placebo-controlled studies (RR 0.71; 95% CI, 0.65 to 0.78 vs. RR 0.84; 95% CI, 0.74 to 0.95, respectively). Thus, PPIs appear to be more effective at relieving symptoms than H2RAs when used for empiric treatment of GERD but the difference in efficacy between these two drug classes narrows when used in specifically patients with NERD.[4] In-class differences between PPIs and H2RAs were not evaluated.

A similar meta-analysis evaluating PPIs was conducted in patients diagnosed with NERD. A total of 6,072 participants were studied in 17 RCTs ranging from 4 weeks to 6 months' duration. Seven studies involving 1,882 participants compared a PPI with a H2RA on the rate of symptomatic relief of NERD which showed PPIs to be significantly superior to H2RAs (RR 1.629; 95% CI, 1.422 to 1.867). The superiority of PPIs was maintained in sub-group analyses comparing short-term with long-term duration of treatment and with high dose PPI compared with low dose. Eleven studies involving 5,416 participants compared a PPI to placebo on the rate of symptomatic relief of NERD which showed PPIs to be significantly superior to placebo (RR 1.903; 95% CI, 1.573 to 2.302), with similar results comparing short-term with long-term duration of treatment and with high dose compared to low dose PPIs. There was no significant difference between PPIs and H2RAs in the rate of adverse events reported in these studies (RR 0.928; 95% CI, 0.776 to 1.110). In addition, there was no significant difference between PPIs and placebo in the rate of adverse events reported (RR 1.000; 95% CI, 0.896 to 1.116). In addition, sub-group analyses comparing short-term with long-term duration of PPI treatment and high dose PPIs compared with low dose PPIs did not reveal a significant difference in reported adverse events relative to placebo. There were no significant differences in rate of symptomatic relief of NERD using higher doses of PPIs (54.4%; 95% CI, 43.3 to 59.5%) versus lower doses (56.3%; 95% CI, 39.5 to 73.2%), nor were there any differences when PPIs were used long-term (51.4%; 95% CI, 43.3 to 59.5) versus short-term (51.5%; 95% CI, 43.2 to 59.8). Unfortunately, lengths of these durations were not explicitly defined. Individual response rates between PPIs were not significantly different (see **table 1**). Unfortunately, results from the meta-analysis are limited by significant heterogeneity between the studies (I^2=96.8%). Only 3 of the 17 RCTs provided adequate sequence generation and no studies adequately concealed allocation. No obvious publication bias was identified.[5]

Table 1. Rate of Symptomatic Relief in Patients with Non-erosive Reflux Disease Treated with Proton Pump Inhibitors.[5]

Proton Pump Inhibitor	Response Rate
Lansoprazole	52.1% (95% CI, 39.2 to 65.0%)
Omeprazole	52.1% (95% CI, 35.5 to 68.8%)
Pantoprazole	44.7% (95% CI, 36.9 to 52.6%)
Rabeprazole	60.8% (95% CI, 36.7 to 84.9%)

Safety of PPIs and H2RAs

Risk of Pre-cancerous Lesions with Long-term Use of PPIs

The safety of long-term use of PPIs is unclear. Long-term acid suppression results in hypergastrinemia, which has been associated with hyperplasia of the enterochromaffin cells lining the digestive tract. Indeed, the risk of development of gastric pre-malignant lesions with use of PPIs is inconsistent in the literature. A Cochrane systematic review was performed in order to assess the association for risk for the development of gastric pre-malignant lesions, such as atrophic gastritis, intestinal metaplasia, enterochromaffin-like cell hyperplasia, and dysplasia, in adult patients on PPIs for at least 6 months. A total of 1,789 participants in 7 RCTs were eligible for inclusion, though none of the studies assessed the development or progression of gastric pre-malignant lesions as a primary outcome. There was no apparent risk for the development of corporal atrophy or corporal intestinal metaplasia with long-term use of PPIs relative to non-PPI users (odds ratio (OR) 1.50; 95% CI, 0.59 to 3.80; p=0.39 and OR 1.46; 95% CI, 0.43 to 5.03; p=0.55, respectively). However, there was a significantly higher risk for the development of either diffuse (simple) (OR 5.01; 95% CI, 1.54 to 16.26; p=0.007) or linear/micronodular (focal) enterochromaffin-like cell hyperplasia (OR 3.98; 95% CI, 1.31 to 12.16; p=0.02) than non-PPI users. None of the included studies reported participants showing any dysplastic or neoplastic changes. There were an inadequate number of studies to assess whether use of PPIs for greater than 1 year was associated with higher risk relative to 6 months of PPI use. Thus, more studies are needed to determine if a significant risk for development of corpus gastric atrophy or intestinal metaplasia exists with long-term use of PPIs since current evidence remains imprecise.[6]

Risk of Adverse Cardiovascular Events with Concomitant Use of PPIs with Clopidogrel

Two systematic reviews recently assessed the concomitant use of clopidogrel with PPIs and its impact on clinical outcomes.[7,8] The FDA published warnings of concomitant therapy of clopidogrel with PPIs, which were initially based on laboratory data and pooled data from retrospective cohort studies limited by substantial heterogeneity and high risk of bias. The former reported reduced *ex vivo* inhibition of platelet aggregation, indicative of a pharmacological interaction between certain PPIs and clopidogrel. Retrospective studies reported adverse clinical outcomes in cases of concomitant therapy, which seemed to correlate with the laboratory data. Clopidogrel is most commonly prescribed in the setting of coronary heart disease, such as acute coronary syndrome or after percutaneous coronary intervention. However, the two meta-analyses did not find any discernable differences in the clinical impact of individual PPIs when used concomitantly with clopidogrel. Each PPI had evidence of statistically significant harm with clopidogrel; however, significant cardiovascular harm was also found in patients on PPIs without clopidogrel relative to populations that do not use a PPI. In both analyses, pooling data solely from RCTs showed no risk of cardiovascular outcomes with concomitant use of PPIs and clopidogrel compared to PPIs users without clopidogrel.[7,8]

The first meta-analysis found a higher incidence of short- and long-term major adverse cardiovascular events (MACE) among patients using PPIs in retrospective studies. Mortality was reported in 23 trials, of which 17 (74%) of them reported no risk difference for patients on PPIs. In the other six studies, the effect ranged from a reduced risk in one study (hazard ratio (HR) 0.68; 95% CI, 0.47 to 0.96) to an increased risk in five studies (RR 2.63; 95% CI, 1.17 to 5.94). Myocardial infarction (MI) was reported in 25 trials, of which 11 (44%) reported a significantly increased RR for PPI users ranging from 1.19 to 4.58. The other 14 studies reported no difference in MI. Of the 25 studies reporting MACE, 12 studies (48%) showed a significantly increased risk when PPIs were combined with clopidogrel, with an effect that ranged from HRs of 1.20 to 4.58. The other 13 studies showed no effect on outcome. Studies specifically evaluating omeprazole and esomeprazole, two PPIs of particular interest due to their role in CYP2C19 metabolism, had significant heterogeneity. Notably, nearly all the prospective studies and, most importantly, the only two trials with random allocation of a PPI, reported no detrimental clinical effect of PPIs in clopidogrel users.[7]

The second meta-analysis found similar findings after evaluating RCTs (n=2), controlled observational studies (n=19) and post-hoc analyses of clinical trials (n=2) reporting MACE in patients receiving clopidogrel. Risk of composite MACE for clopidogrel and individual PPIs were similar. Omeprazole was associated with an OR of 1.24 (95% CI, 1.07 to 1.43) with significant heterogeneity (I^2=74%); esomeprazole was associated with an OR of 1.32 (95% CI, 1.09 to 1.60) with significant heterogeneity (I^2=76%); lansoprazole was associated with an OR of 1.39 (95% CI, 1.23 to 1.57) with less heterogeneity (I^2=26%); pantoprazole was associated with an OR of 1.41 (95% CI, 1.21 to 1.64), also limited by significant heterogeneity (I^2=75%); and rabeprazole was associated with a nonsignificant OR of 1.38 (95% CI, 0.78 to 2.45), also limited by significant heterogeneity (I^2=76%). There was no evidence for any consistent difference between PPIs and the risk of MI or other major adverse cardiac events. A significant cardiovascular risk was found with PPI use alone compared to patients not receiving clopidogrel or PPIs (OR 1.28; 95% CI, 1.14 to 1.44; I^2=77%). The significant heterogeneity between studies that described the cardiovascular effects of PPIs in the absence of clopidogrel stemmed from one study; however, the risk of PPI use alone remained significant even without the study included (OR 1.39; 95% CI, 1.32 to 1.46). But like the previous meta-analysis, when a sensitivity analysis was performed on RCTs, the pooled OR for MACE was no longer statistically significant (OR 1.04; 95% CI, 0.72 to 1.51; p=0.83 vs. OR 0.94; 95% CI, 0.47 to 1.87; p=0.87, respectively).[8]

Risk of Clostridium difficile Infection with Use of H2RAs

A meta-analysis was performed to assess the association between H2RA use and *Clostridium difficile* infection (CDI).[9] The role of gastric acid suppression has recently gained interest as a risk factor for CDI. Earlier meta-analyses suggested an association between PPIs and CDI and the FDA issued a safety alert for possible increased risk of CDI with chronic PPI use in 2012.[10] Any analytical study examining the association between H2RAs and the incidence of CDI in the adult population was eligible for inclusion in this meta-analysis. Thirty-five observations from 33 eligible studies were pooled using a random effects model. Most studies did not specify the type or duration of H2RA therapy. The pooled effect estimate was 1.44 (95% CI, 1.22 to 1.70; I^2=70.5%). The pooled effect estimate for high quality studies was 1.39 (95% CI, 1.15 to 1.68; I^2=72.3%). This association was consistent across different subgroups (by study design and country) and there was no evidence of publication bias. The number needed to harm (NNH) with H2RAs in the general population at 1 year was 4549 persons (95% CI, 2860 to 9097). The NNH with H2RAs at 14 days after hospital admission in patients receiving antibiotics was 58 persons (95% CI, 37 to 115), whereas the NNH was 425 persons (95% CI, 267 to 848) if they did not receive antibiotics. Therefore, risk of CDI is low overall with H2RAs but risk is highest in hospitalized patients receiving antibiotics.[9]

Subpopulations

Decreased Risk of Esophageal Adenocarcinoma with PPIs in Patients with Barrett's Esophagus

This incidence of esophageal adenocarcinoma (EAC) has increased by more than six-fold in the last 30 years. Barrett's esophagus (BE) is a precursor lesion for EAC and confers a 30-125-fold higher risk of EAC. Preclinical studies indicate PPIs may prevent or delay progression of dysplasia in BE. At the same time, PPI-related acid suppression-induced hypergastrinemia and subsequent proliferation have led to concerns about the oncogenic potential of long-term PPI therapy. The primary analysis of this systematic review focused on assessing the risk of progression to EAC and/or high-grade dysplasia (BE-HGD) in patients with BE among PPI users (and H2RA users) compared with non-users.[11] Seven observational studies (five cohort, two case-control studies) were identified that reported on the association between PPIs and risk of EAC and/or BE-HGD and two observational studies (one cohort and one case-control) reporting on the association between H2RAs and these outcomes. Use of a PPI at the time of BE diagnosis was associated with a decreased risk of EAC and/or BE-HGD in patients with BE (unadjusted OR 0.26; 95% CI, 0.10 to 0.71). This protective effect persisted when adjusted for concomitant use of NSAIDs, aspirin or statins (adjusted OR 0.44; 95% CI, 0.24 to 0.83) as well as presence of erosive esophagitis or reflux symptoms (adjusted OR 0.15; 95% CI, 0.04 to 0.55). Long-term exposure to PPIs (>2-3

years) was associated with a greater protective effect on EAC and/or BE-HGD risk (adjusted OR 0.45; 95% CI, 0.19 to 1.06) whereas short-term exposure (<2-3 years) was not significantly associated with EAC and/or BE-HGD (adjusted OR 1.09; 95% CI, 0.47 to 2.56). The observed cumulative incidence rates of EAC and/or BE-HGD in patients with BE overall, non-dysplastic BE and BE with low grade dysplasia were 10.2, 6.8 and 18.3 per 1000 patient-years, respectively. There was insufficient data from these studies to allow estimation of PPIs' effect on risk of progression to EAC alone or BE-HGD alone. There were also insufficient data to allow pooling based on type, dose or frequency of use of PPIs. In addition, there was considerable heterogeneity in the overall analysis (I^2=81%). Recently, two nested case-control studies resulted in observational evidence that conflicts with this meta-analysis, adding a level of ambiguity to the role of PPIs in BE.[12,13] Two studies reported on the association between H2RA use and the risk of EAC in patients with BE but neither of them individually observed a protective association.[11]

PPIs and H2RAs in the Pediatric Population

The natural history of gastro-esophageal reflux in infancy is generally that of a functional, self-limiting condition that improves with age; less than 5% of children with vomiting or regurgitation continue to have symptoms after infancy. Older children and children with co-existing medical conditions may have a much longer course of symptoms. A Cochrane systematic review was performed in order to provide a robust analysis of currently available pharmacological interventions used to treat children with gastro-esophageal reflux. All safety and efficacy outcomes studied in RCTs on study participants from birth to 16 years of age were assessed with a primary focus on improvement in clinical symptoms. A total of 1,201 participants were studied in 24 trials 4-8 weeks in length, most of which received pharmaceutical industry support for manuscript preparation. Most of the studies assessing PPIs and H2RAs enrolled children greater than 12 months of age with limited evidence in children under 1 year of age. In addition, several different endpoints were assessed, study design varied, and study populations were heterogeneous in these trials precluding the ability for the authors to perform a meta-analysis of the data. In general, moderate-quality evidence suggested from these trials that PPIs can reduce gastro-esophageal reflux symptoms in children with confirmed erosive esophagitis, improve pH metrics and improve erosive changes on endoscopy, particularly in older children. No PPIs demonstrated statistical superiority over another PPI and evidence is weaker for the use of PPIs in infants. Evidence also suggested that H2RAs can reduce symptoms but methodological differences between studies evaluating H2RAs make it difficult to assess efficacy overall. One study showed high dose ranitidine was comparable to omeprazole in symptom relief, pH indices and endoscopic findings. The addition of a H2RA to a PPI did not offer additional improvement in symptoms. No serious adverse events were noted in the trials. Overall, evidence supports the short-term use of PPIs in children with gastro-esophageal symptoms. Evidence for the use of H2RAs other than ranitidine is more limited, however, and use of either of these drug classes is limited in infants. No within class differences in efficacy or safety were demonstrated.[14]

PPIs and H2RAs in the Cystic Fibrosis Population

Impaired pancreatic function in patients with cystic fibrosis (CF) may result in increased gastric acidity, leading to heartburn, risk for development of peptic ulcers and impairment of oral pancreatic enzyme replacement therapy. Orally administered pancreatic enzymes may be inactivated by gastric acid in people with CF with pancreatic insufficiency leading to fat and protein malabsorption. The administration of gastric acid-reducing agents such as PPIs and H2RAs have been used as an adjunct to pancreatic enzyme therapy to improve absorption of fat and GI symptoms in patients with CF. A Cochrane systematic review was performed in order to establish the evidence regarding potential benefits and safety of PPIs and H2RAs in CF. Primary outcomes included nutritional status as assessed by weight, height and other indices of growth; symptoms related to increased gastric acidity such as epigastric pain or heartburn; and complications of increased gastric acidity such as gastric or duodenal ulcers. Secondary outcomes included measures of fat absorption, lung function, quality of life, mortality and adverse effects related to these drugs. A total of 273 participating children and adults in 17 RCTs were eligible for inclusion: seven trials were limited to children and four trials were limited only to adults. Most trials were placebo-controlled but unfortunately, study design and insufficient data from these trials prohibited

a meta-analysis from being conducted. Two placebo-controlled H2RA trials measured nutritional status which showed no significant improvements in height, weight and skinfold thickness between the treatment and control groups. Nine trials measured GI symptoms but none of the trials assessing a PPI or H2RA reported results. No trials assessed long-term complications of increased gastric acidity such as gastric or duodenal ulcers. For secondary outcomes, 7 trials reported significant improvement in measures of fat malabsorption; and two trials reported no significant improvement in nutritional status. No trials were identified assessing the effectiveness of PPIs or H2RAs in improving quality of life, long-term complications of increased gastric acidity or mortality. Lung function was reported to improve only narratively in two trials. Thus, limited evidence suggests PPIs and H2RAs in CF patients result in improvement in GI symptoms and fat absorption but there is insufficient evidence to suggest these drugs have an effect on nutritional status, lung function, quality of life or mortality. Participants in studies assessing PPIs and H2RAs tolerated the drugs well; only one participant was forced to withdraw from a study because of possible neurological complications due to cimetidine.[15]

New Guidelines:

National Institute for Health and Care Excellence

In 2014, NICE developed guidance for the management of dyspepsia and symptoms suggestive of GERD. Dyspepsia in primary care is broadly defined to include people with recurrent epigastric pain, heartburn or acid reflux, with or without bloating, nausea or vomiting. According to the guideline, lifestyle changes are core to the treatment of dyspepsia, which includes healthy eating, weight loss and smoking cessation. Known precipitants of dyspepsia should be avoided if possible, including smoking, alcohol, coffee, chocolate, fatty foods and being overweight. Alternative therapy to medications known to cause dyspepsia (see **table 2**) should be considered.[1]

8

Table 2. Drugs Associated with Increased Risk of Dyspepsia.[1]

Calcium Channel Blockers	Nitrates	Theophylline	Bisphosphonates	Corticosteroids	Non-steroidal Anti-inflammatory Drugs

Empirical, standard-dose PPI therapy for 4 weeks should be offered to patients with dyspepsia. Dosing of PPIs using language described by NICE are defined in **table 3**. Choice of a PPI should be based on cost, tolerability of the PPI, possible interactions with other drugs, and patient preference. Patients receiving PPI therapy for dyspepsia symptoms should reduce therapy to the lowest effective dose and reduce frequency by trying "as-needed" use when appropriate, and returning to self-treatment with an antacid. Patients who need long-term management of dyspepsia symptoms should have their condition reviewed annually and be encouraged to try stepping down or stopping therapy unless there is an underlying condition that necessitates continuing treatment.[1]

Table 3. Proton Pump Inhibitor Doses Relating to NICE Evidence Synthesis and Recommendations.[1]

Proton Pump Inhibitor	Standard Dose	Low Dose (on demand)	Double Dose
Esomeprazole	20 mg once daily	Not available	40 mg once daily
Lansoprazole	30 mg once daily	15 mg once daily	30 mg twice daily
Omeprazole	20 mg once daily	10 mg once daily	40 mg once daily
Pantoprazole	40 mg once daily	20 mg once daily	40 mg twice daily
Rabeprazole	20 mg once daily	10 mg once daily	20 mg twice daily

Patients with a diagnosis of GERD should be managed similarly to uninvestigated dyspepsia and be offered a standard-dosed PPI for 4 or 8 weeks. Again, the dose should be tapered to the lowest effective dose and patients are encouraged to manage symptoms only when needed. Patients with severe esophagitis should be given a standard-dose PPI for 8 weeks to allow for adequate healing. If initial treatment for healing severe esophagitis fails, switching to another standard-dose PPI or increasing the current PPI to a double-dose regimen may be considered, though evidence is lacking. In cases of severe esophagitis, long-term maintenance therapy of a standard-dose PPI may be required.[1]

If the patient is diagnosed with PUD secondary to *Helicobacter pylori*, the bacteria must be eradicated using recommended 7-day therapy including a PPI, amoxicillin and either clarithromycin or metronidazole. However, if the patient has a NSAID-induced peptic ulcer, the NSAID must be discontinued and the patient started on a standard-dose PPI or H2RA therapy for 4 to 8 weeks. For patients continuing to take NSAIDs after a peptic ulcer is healed, the potential harms from NSAID treatment should be discussed and the need for NSAID treatment should be reviewed at least every 6 months with the patient. Reducing the dose of the NSAID, switching to a COX 2-selective NSAID, substituting the NSAID with acetaminophen or switching to low dose ibuprofen should be considered. A PPI should be continued indefinitely in all patients on NSAIDs at high risk for NSAID-induced ulcers (i.e., previous ulcers).[1]

National Institute for Health and Care Excellence

In 2015, NICE developed guidance for the management of GERD in children. According to the guideline, gastro-esophageal reflux is a normal physiological process that usually happens after eating in healthy infants and children. In contrast, GERD occurs when the effect of the reflux leads to symptoms severe enough to merit medical treatment. In clinical practice, the terms gastro-esophageal reflux and GERD are used interchangeably in this population and there is no reliable and accurate diagnostic test to confirm whether the condition is simply gastro-esophageal reflux or GERD. In no wise are acid-suppressing drugs, such as PPIs or H2RAs ever recommended to treat overt regurgitation in infants and children occurring as an isolated symptom. Several non-pharmacological management options are presented in the guideline, depending on the age and circumstances of the infant or child, and should be initiated before starting medicine in this population. A 4-week trial of a PPI or H2RA may be considered for those who are unable to describe their symptoms (e.g., infants or young children) and have overt regurgitation with at least one of the following: unexplained feeding difficulties (e.g., refusing feeds, gagging or choking); distressed behavior; or delayed growth. In addition, a 4-week trial of a PPI or H2RA may be considered in children and young people with persistent heartburn, retrosternal pain or epigastric pain. In all cases, response to therapy should be assessed at 4 weeks and the patient referred to a specialist or endoscopy if symptoms have not resolved or recur after stopping treatment. A PPI or H2RA should be continued in patients with endoscopy-proven reflux esophagitis along with continued reassessments.[16]

The American Journal of Gastroenterology

The American Journal of Gastroenterology published a guideline for the diagnosis and management of GERD in adults in 2013. The GRADE system was used to evaluate the strength of the recommendations and the overall level of evidence. Similar non-pharmacological measures are recommended in the management of GERD, including weight loss and routine elimination of foods known to trigger reflux. An 8-week course of PPIs is the therapy-of-choice for symptom relief and healing of erosive esophagitis (*Strong Recommendation, High Level of Evidence*). There are no major differences in efficacy between different PPIs (*Strong Recommendation, High Level of Evidence*). Therapy with a PPI should be initiated at once daily dosing, before the first meal of the day (*Strong Recommendation, Moderate Level of Evidence*). For patients with a partial response to once daily therapy, tailored therapy with adjustment of dose timing or twice daily dosing should be considered in patients with night-time symptoms, variable schedules, or sleep disturbance (*Strong Recommendation, Low Level of Evidence*). In

patients with partial response to PPI therapy, increasing the dose to twice daily therapy or switching to a different PPI may provide additional symptom relief (*Conditional Recommendation, Low Level of Evidence*). Maintenance PPI therapy should be administered for GERD patients who continue to have symptoms after a PPI is discontinued and in patients with complications including erosive esophagitis and Barrett's esophagus (*Strong Recommendation, Moderate Level of Evidence*). For patients who require long-term PPI therapy, it should be administered at the lowest effective dose, including "as needed" or intermittent therapy (*Conditional Recommendation, Low Level of Evidence*). Treatment with a H2RA can be used as a maintenance option in patients without erosive disease if patients experience heartburn relief (*Conditional Recommendation, Moderate Level of Evidence*). Bedtime H2RA therapy can be added to daytime PPI therapy in selected patients with objective evidence of night-time reflux if needed, but H2RAs may be associated with the development of tachyphylaxis after several weeks of use (*Conditional Recommendation, Low Level of Evidence*).[17]

<u>The European Association of Endoscopic Surgery</u>

The European Association of Endoscopic Surgery issued a consensus statement on recommendations for the management of GERD. A Grade of Recommendation (GoR) was assigned based on a recommendation's level of evidence (A = 'must'; B = 'should'; C = 'can'). The degree of consensus was also expressed as the percentage of agreement for a certain recommendation by the expert panel (ExC) and the scientific community (SCC).[2]

According to the guideline, GERD (including ERD and NERD) is associated with significant impairment of quality of life. Thus, the goals of medical therapy in GERD are to control heartburn, heal gastroesophageal injuries and improve quality of life (*GoR A; ExC 100%; SCC 100%*). Acid suppressive drugs such as PPIs and H2RAs are effective in patients with esophageal syndromes. However, PPIs are more powerful than H2RAs in providing mucosal healing and symptomatic relief (*GoR A; ExC 100%; SCC 100%*). Though H2RAs continue to be a mainstay of GERD treatment, H2RAs have shown lower efficacy than PPIs in acid suppression, but given in divided doses may be effective in some patients with less severe forms of GERD. However, it is important to note that continuous use of H2RAs is associated with the development of tachyphylaxis, thus limiting their long-term use and efficacy. Proton pump inhibitors potently reduce gastric acid secretion and provide the most powerful symptomatic relief and heal esophagitis in the majority of patients. Standard doses of omeprazole, lansoprazole, pantoprazole, esomeprazole and rabeprazole have shown comparable rates of healing and remission of erosive esophagitis. In patients with a partial or unsatisfactory response to a once daily PPI dose, twice daily PPI dosing may help improve symptom relief (*GoR B; ExC 100%; SCC 98%*). Data supporting twice daily dosing of PPIs and H2RAs rather than standard dosing for improving mucosal healing and symptom relief are weak and largely based on expert opinion. The current treatment for Barrett's esophagus includes PPIs in single or double doses or antireflux surgery and aims to control GERD-related symptoms and to prevent complications such as ulcers, bleeding and strictures. However, antireflux surgery may be more effective than medical therapy for Barrett's esophagus and should be considered, particularly in young patients (*GoR C; ExC 100%; SCC 89%*). Antireflux surgery has the advantage of correcting LES failure and the frequently associated hiatal hernia, as well as controlling abnormal gastric and duodenal reflux in 80-90% of patients. However, some data suggests escalating PPI doses may have a comparable rate of symptom control as surgery.[2]

New Safety Alerts:

New FDA PPI labeling additions to CONTRAINDICATIONS, WARNINGS and PRECAUTIONS include hypersensitivity reactions resulting in acute interstitial nephritis and cyanocobalamin (vitamin B-12) malabsorption leading to nutritional deficiency secondary to daily long-term use (e.g., longer than 3 years). **Table 4** lists current FDA safety alerts found in PPI labeling.

Table 4. Current FDA Safety Alerts for Proton Pump Inhibitors.

FDA Safety Alert	
***Clostridium difficile*-associated diarrhea**	PPIs may be associated with an increased risk of *Clostridium difficile*–associated diarrhea (CDAD). A diagnosis of CDAD should be considered for patients taking PPIs who develop diarrhea that does not improve.
Low magnesium levels	Prescription PPIs may cause low serum magnesium levels (hypomagnesemia) if taken for prolonged periods of time (in most cases, longer than one year). In approximately one-quarter of the cases reviewed, magnesium supplementation alone did not improve low serum magnesium levels and the PPI had to be discontinued.
Cyanocobalamin (vitamin B-12) deficiency	Daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12) caused by hypo- and achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed.
Acute interstitial nephritis	Acute interstitial nephritis has been observed in patients taking PPIs. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to idiopathic hypersensitivity reaction. Discontinue the PPI if acute interstitial nephritis develops.
Bone fractures	Several published observational studies in adults suggest that PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (1 year or longer). Patients should use the lowest and shortest duration of PPI therapy appropriate for the condition being treated.

New Formulations or Indications:
None identified.

Randomized Controlled Trials:

One relevant clinical trial was identified from the literature search (see **Table 5**). The full abstract is included in **Appendix 2**.

Table 5. Description of Randomized Comparative Clinical Trials

Study	Comparison	Population	Primary Outcome	Results	Quality*
Moraes-Filho, et al. MC, DB, PG, RCT	Pantoprazole 40 mg/day vs. Esomeprazole 30 mg/day for 4 weeks	Adults w/ erosive GERD	Complete remission of GERD at 4 weeks based on confirmed endoscopic healing and relief of symptoms based on ReQuest-GI questionnaire, which assesses GI-related symptoms associated with GERD	Pantoprazole 170/278 (61.2%) Esomeprazole 165/270 (61.1%) P = not significant	Good

Abbreviations: DB = double blind; GERD = gastro-esophageal reflux disease; GI = gastrointestinal; MC = multi-centered; PG = parallel group; RCT = randomized controlled trial
*Quality of each study is ranked as "Good", "Fair" or "Poor" based on DURM Standard Methods for Quality Assessment and Grading the Evidence.

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Appendix 1: Current Status on Preferred Drug List

Preferred	**Non-Preferred**
Proton Pump Inhibitors	
Omeprazole capsule Pantoprazole tablet	Dexlansoprazole Esomeprazole Lansoprazole Omeprazole packet; suspension; tablet Omeprazole/sodium bicarbonate Pantoprazole packet Rabeprazole
Histamine-2 Receptor Antagonists	
Cimetidine tablet Famotidine tablet Ranitidine syrup, tablet	Cimetidine solution Famotidine suspension Famotidine/calcium carbonate/magnesium hydroxide Nizatidine Ranitidine capsule; tablet

Appendix 2: Abstracts of Clinical Trials

Moraes-Filho J, Pedroso M and Quigley E. Randomised clinical trial: daily pantoprazole magnesium 40 mg vs. esomeprazole 40 mg for gastro-oesophageal reflux disease, assessed by endoscopy and symptoms. *Alimentary Pharmacology and Therapeutics*. 2014; 39: 47-56.

Background:
Pantoprazole magnesium (pantoprazole-Mg) may display extended inhibi-tion of the proton pump with the potential for improved clinical efficacy in gastro-oesophageal reflux disease (GERD).
Aim:
To compare the efficacy of pantoprazole-Mg and esomeprazole in GERD.
Methods:
Gastro-oesophageal reflux disease (Los Angeles grades A–D) patients were randomised to 4 weeks of treatment with pantoprazole-Mg (n=290) or esomeprazole (n=288), both 40 mg once daily, in this multicentre (14 Brazilian sites in 9 cities), double-blind study, with an additional 4 weeks' treatment in non-responding patients. Severity of oesophagitis (at endoscopy) and GERD-related symptoms (ReQuest-GI) were assessed. The primary end point was the proportion of patients in complete remission (ReQuest-GI score < 1.73 plus endoscopic healing) at week 4.
Results:
Complete remission occurred in 61% of patients in each treatment group at 4 weeks (primary endpoint) and in 81% and 79% of patients in the pantoprazole-Mg and esomeprazole groups at 8 weeks, with no significant differences. Mucosal healing rates were high and not significantly different. At 8 weeks, symptom relief with pantoprazole-Mg was significantly greater than that with esomeprazole (91.6% vs. 86.0%, P=0.0370) because of continued improvement in symptoms with pantoprazole-Mg from week 4 to week 8 (P=0.0206).
Conclusions:
Pantoprazole-Mg 40 mg was at least as effective as esomeprazole 40 mg for complete remission and the mucosal healing rate was high. Symptom relief with pantoprazole-Mg continued to improve from 4 to 8 weeks and was greater than that with esomeprazole at week 8, suggesting an extended period of treatment effect.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to January Week 3 2015

1 exp Omeprazole/ 6374
2 pantoprazole.mp. 1287
3 exp Dexlansoprazole/ 45
4 exp Esomeprazole/ 704
5 exp Lansoprazole/ 1651
6 exp Rabeprazole/ 771
7 1 or 2 or 3 or 4 or 5 or 6 7664
8 limit 7 to (english language 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 randomized controlled trial)) 39

Ovid MEDLINE(R) without Revisions 1996 to January Week 3 2015

1 exp Cimetidine/ 1442
2 exp Famotidine/ 729
3 exp Ranitidine/ 1815
4 exp Nizatidine/ 124
5 1 or 2 or 3 or 4 3730
6 limit 5 to (english language and yr="2013 -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 randomized controlled trial)) 31

Drug Use Research & Management Program
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Drug Use Evaluation: Proton Pump Inhibitor (PPI) /Histamine-2 Receptor Antagonist (H2RA) Length of Therapy

The Health Evidence Review Committee (HERC) placed long-term (>8 weeks) medical treatment of gastro-esophageal reflux disease (GERD) below the funding line effective January 1, 2015.[1] Dyspepsia is also a non-funded condition. Other Food and Drug Administration (FDA) approved indications for PPIs and H2RAs remain funded. PPIs and H2RAs were associated with close to $500,000 annual net cost in the fee-for-service (FFS) program and $2.13 million annual net cost in the coordinated care organizations during calendar year 2014.

The goal of this drug use evaluation is to quantify the long-term use (>8 weeks) of PPIs and H2RAs in terms of volume and associated diagnosis funding to inform policy options.

Methods:

A cross-section of all patients with a single paid fee-for-service (FFS) drug claim for a drug in the PPI, H2RA or *H. pylori* Drugs classes during calendar year in 2014 were included. Patients were excluded if they were covered by Medicare Part D as defined by the benefit package BMM or BMD. Patients were also excluded if they were eligible fewer than 274 days in CY 2014.

The first claim in 2014 (including encounter drug claims) for any drugs of interest was identified as the index claim. Spans of continuous therapy on any drug (i.e. multiple drugs serially) from included classes with a maximum gap of 15 days for each patient were determined. Patients with less than 60 days of continuous therapy were excluded.

For all remaining patients, the diagnoses groups in **Appendix 1** were flagged if present 1 year prior to the index claims and throughout CY2015 year to date, in either encounter or FFS claims.

Results:

Table 1 displays patient selection flow. Approximately 75% (n=5944) of patients meeting eligibility criteria used antiulcer drugs for 60 days or longer. **Table 2** displays the demographics of long-term acid suppressant users which are predominantly adults. **Table 3** indicates 93.3% of patients are treated first with a preferred drug and is most often a PPI (>85%). **Table 4** reveals funded conditions are associated with just 14-16% of long-term users, there was no diagnosis of interest associated with 44-45% of patients and 39-42% of long-term patients were associated with non-funded diagnoses only. Finally, **Table 5** summarizes the average length of therapy spans (230 days), unique drugs used during the span (1) and average cost of therapy per patient ($166) and $24 per claim.

Table 1 – Patient Selection

Criteria	Remaining	Lost
Non Medicare patients with selected FFS claim in CY 2014 for PPI, H2RA, *H pylori*:	7,605	
Patients with >=75% eligibility in CY 2014	6,712	893
Patients with spans >= 60 days	5,944	1,661

Table 2 – Demographics

	All Patients		Patients on >= 60 days continuous Tx		Patients on multiple Tx spans (none >=60 days)	
N=	6,712	%	4,306	%	745	%
Mean age (range)	39.0	(0-92)	42.1	(0-92)	37.1	(0-70)
< 19	961	14.3%	471	10.9%	113	15.2%
19-64	5,711	85.1%	3,809	88.5%	629	84.4%
> 64	40	0.6%	26	0.6%	3	0.4%
Female	4,223	62.9%	2,661	61.8%	474	63.6%
Caucasian	4,773	71.1%	3,189	74.1%	517	69.4%

Table 3 – Index Drug Distribution

Class			All Patients		Patients on >= 60 days continuous Tx		Patients on multiple Tx spans (none >=60 days)	
Group	**Brand Name***	**N=**	6,712	%	4,306	%	745	%
PPI	DEXILANT		11	0.2%	10	0.2%	1	0.1%
PPI	FIRST-OMEPRAZOLE		41	0.6%	27	0.6%	3	0.4%
PPI	LANSOPRAZOLE		45	0.7%	38	0.9%	2	0.3%
PPI	NEXIUM		62	0.9%	50	1.2%	6	0.8%
PPI	OMEPRAZOLE		4,867	72.5%	3,143	73.0%	547	73.4%
PPI	PANTOPRAZOLE SODIUM		773	11.5%	515	12.0%	81	10.9%
PPI	PREVACID		63	0.9%	56	1.3%	3	0.4%
PPI	PROTONIX		15	0.2%	14	0.3%		0.0%
H2A	ACID REDUCER		17	0.3%	10	0.2%		0.0%
H2A	CIMETIDINE		48	0.7%	21	0.5%	2	0.3%
H2A	FAMOTIDINE		107	1.6%	67	1.6%	13	1.7%
H2A	RANITIDINE HCL		623	9.3%	328	7.6%	83	11.1%

* Only drugs with >10 patients are displayed

Table 4 – Diagnoses Groups Associated with Long-Term Acid Suppressant User

	All Patients		Patients on >= 60 days continuous Tx		Patients on multiple Tx spans (none >=60 days)	
N=	6,712	%	4,306	%	745	%
Dx Group 1 - Non-funded Dx only	2,612	38.9%	1,822	42.3%	289	38.8%
Dx Group 2 - Funded Dx	330	4.9%	175	4.1%	37	5.0%
Dx Group 3 - Severe Dx, Funded	0	0.0%	2	0.0%	0	0.0%
Dx Group 1 + (2 or 3)	597	8.9%	428	9.9%	83	11.1%
No Dx from any group	3,169	47.2%	1,877	43.6%	336	45.1%

Table 5 – Drug Use Description by Index Drug

Class Group	Brand Name*	N=	Patients on >= 60 days continuous Tx		Sum of days drug available		Unique Drug count per patient		Total cost^ of drugs of interest per patient		Total claim count on drugs of interest per patient	
			4,306	%	Mean	(Range)	Mean	(Range)	Mean	(Range)	Mean	(Range)
	All patients combined		4,306	100.0%	230	(42-1110)	1.15	(1-5)	$166	(0-10232.59)	7.1	(1-37)
PPI	DEXILANT		10	0.2%	283	(60-630)	1.30	(1-3)	$1,634	(373.22-5175.71)	8.6	(2-21)
PPI	FIRST-OMEPRAZOLE		27	0.6%	170	(60-349)	1.26	(1-2)	$736	(55.22-7550.28)	6.4	(2-19)
PPI	LANSOPRAZOLE		38	0.9%	299	(60-450)	1.37	(1-3)	$383	(0-2539.73)	10.0	(2-15)
PPI	NEXIUM		50	1.2%	273	(60-720)	1.28	(1-4)	$2,301	(0-10232.59)	9.0	(2-24)
PPI	OMEPRAZOLE		3,143	73.0%	224	(56-870)	1.09	(1-3)	$93	(0-3420.93)	6.9	(1-29)
PPI	PANTOPRAZOLE SODIUM		515	12.0%	241	(42-840)	1.25	(1-5)	$117	(0-4746.1)	7.4	(1-28)
PPI	PREVACID		56	1.3%	285	(90-420)	1.07	(1-2)	$1,984	(0-6444.24)	10.1	(3-21)
PPI	PROTONIX		14	0.3%	263	(60-360)	1.57	(1-2)	$269	(26.03-1204.01)	8.8	(2-14)
H2A	ACID REDUCER		10	0.2%	187	(60-270)	1.50	(1-2)	$94	(18.13-199.29)	5.7	(1-10)
H2A	CIMETIDINE		21	0.5%	216	(60-1110)	1.43	(1-3)	$113	(14.32-618.66)	6.7	(2-37)
H2A	FAMOTIDINE		67	1.6%	237	(60-570)	1.46	(1-3)	$83	(0-704.81)	7.7	(2-19)
H2A	RANITIDINE HCL		328	7.6%	241	(56-810)	1.35	(1-4)	$140	(0-3407.87)	8.1	(1-26)

* On brands with 10 or more patient displayed ^Reimbursed pharmacy cost not including rebates

Discussion/Recommendations:

There is significant long-term (>8 weeks) use of PPIs in the OHP FFS population (75% of acid-suppressant users). Less than 16% of long-term PPI users are associated with funded diagnoses.

1) Maintain open access of preferred H2RAs due to their low overall utilization, low cost and established safety profiles.
2) Continue open access of preferred PPIs for up to 60 days to allow for short-term treatment of GERD and *H. pylori*.
3) Establish new Prior Authorization (PA) criteria to encourage use of preferred PPIs and limit use of all PPIs for more than 60 days to conditions funded by OHP (see **Appendix 2**).
4) Grandfather current long-term PPI users to phase-in implementation.
5) Implement broad education outreach to prescribers before applying new criteria.
6) Recommend re-evaluating policy 1 year after implementation.

Appendix 1: Diagnoses of Interest

1) Non-funded Dx	
Dyspepsia	5368x
Esophagitis	53010 - 53019
Ulcer of esophagus	5302x
Diverticulum of esophagus, acquired	5306x
Esophageal reflux	53081
Esophageal leukoplakia	53083
Barrett's esophagus	53085
Unspecified disorder of esophagus	53089-5309x
2) Funded Dx	
Achalasia and cardiospasm	5300x
Stricture & Stenosis of Esophagus	5303x
Perforation of Esophagus	5304x
Dyskinesia of esophagus	5305x
Gastro-esophageal laceration-hemorrhage syndrome	5307x
Esophageal hemorrhage	53082
Gastric Ulcer	5310x - 53191
Duodenal Ulcer	5320x - 53291
Peptic ulcer, site unspecified	5330x - 53391
Gastrojejunal ulcer	5340x - 53491
Gastritis and duodenitis	5350x - 53571
3) Severe Dx	
Zollinger-Ellison	2515x
Neoplasm of uncertain behavior of other and unspecified endocrine glands	2374x
Malignant mast cell tumors	2026x
Multiple endocrine neoplasia [MEN] type I	25801

Proton Pump Inhibitors (PPIs)

Goals:

- Promote PDL options
- Restrict PPI use to patients with OHP-funded conditions

Requires PA:

- Preferred PPIs beyond 60 days' duration
- Non-preferred PPIs

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org
- Individual components for treatment of *H. pylori* that are preferred products

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is the request for a preferred PPI?	Yes: Go to 5	No: Go to 3
3. Is the treating diagnosis an OHP-funded condition?	Yes: Go to 4	No: Pass to RPh. Deny; not funded by OHP.
4. Will the prescriber consider changing to a preferred PPI product? Message: Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	Yes: Inform prescriber of covered alternatives.	No: Go to 7
5. Has the patient already received 60 days of PPI therapy and is the diagnosis: • GERD [esophageal reflux (53081), esophagitis (53010 – 53019)] or • *H. pylori* infection (04186)?	Yes: Go to 6	No: Go to 7
6. Does the patient have recurrent, symptomatic erosive esophagitis that has resulted in previous emergency department visits or hospitalizations?	Yes: Approve for 1 year	No: Pass to RPh. Deny; medical appropriateness. Message: Patient has received a full course of OHP-funded treatment.
7. Are the indication, daily dose and duration of therapy consistent with criteria outlined in **Table 1**? Message: OHP-funded conditions are listed in **Table 1**. A current list of funded conditions is available at: http://www.oregon.gov/oha/herc/Pages/PrioritizedList.aspx	Yes: Approve for recommended duration.	No: Pass to RPh. Deny; medical appropriateness or not funded by OHP

Table 1. Dosing and Duration of PPI Therapy for OHP Funded Conditions.

Funded OHP Conditions*	Maximum Duration	Maximum Daily Dose
GERD: Esophageal reflux (53081) Esophagitis (5301x)	8 weeks* *Treatment beyond 8 weeks is not funded by OHP.	Dexlansoprazole 30 mg Esomeprazole 20 mg Lansoprazole 15 mg Omeprazole 20 mg Pantoprazole 40 mg Rabeprazole 20 mg
H. pylori Infection (04186)	2 weeks	
Achalasia and cardiospasm (5300x) Stricture & Stenosis of Esophagus (5303x) Perforation of Esophagus (5304x) Dyskinesia of esophagus (5305x) Gastroesophageal laceration-hemorrhage syndrome (5307x) Esophageal hemorrhage (53082) Gastric Ulcer (5310x – 53191) Duodenal Ulcer (5320x – 53291) Peptic ulcer site unspecified (5330x – 53391) Gastrojejunal ulcer (5340x – 53491) Gastritis and duodenitis (5350x – 53571) Zollinger-Ellison (2515x) Neoplasm of uncertain behavior of other and unspecified endocrine glands (2374x) Malignant mast cell tumors (2026x) Multiple endocrine neoplasia [MEN] type I (25801)	1 year	Dexlansoprazole 60 mg Esomeprazole 40 mg Lansoprazole 60 mg Omeprazole 40 mg Pantoprazole 80 mg Rabeprazole 40 mg

*A current list of funded conditions is available at: http://www.oregon.gov/oha/herc/Pages/PrioritizedList.aspx

P&T / DUR Action: *3/15 (AG), 1/13, 2/12, 9/10, 3/10, 12/09, 5/09; 5/02; 2/02; 9/01, 9/98*
Revision(s) *2/15, 5/13, 5/12, 1/11, 4/10, 1/10; 9/06, 7/06, 10/04, 3/04*
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High Dose Opioid Drug Use Evaluation

Background

Concerns over misuse and abused of opioid analgesics have garnered national and regional attention. In 2011 the Executive Office of the President stated: "Prescription drug misuse and abuse is a major public health and public safety crisis."[1] The Director of the Center for Disease Control (CDC) described misuse and abuse of prescriptions as an "epidemic."[2] The Centers for Medicare and Medicaid Services (CMS) in 2011 indicated that Prior Authorizations are a part of a "robust state controlled prescription drug program." Washington State enacted House Bill 2876 mandating pain specialist consultations for patients exceeding 120 morphine equivalents daily (MED).[3]

The use of long-acting opioids (LAO) has been steadily increasing despite concerns over efficacy and safety. Medicaid prescriptions for opioids doubled between 1998 and 2003, accounting for approximately 4% of all Medicaid prescriptions by 2003.[4] With increasing use of LAO there has been a corresponding increase in morbidity, as illustrated by an increasing number of emergency department (ED) visits. The Drug Abuse Warning Network (DAWN) studied ED visits from 2004-2008 and saw a 111% increase in visits related to nonmedical use of opioid analgesics. Methadone, oxycodone and hydrocodone use were associated with the highest number of visits. The non-medical use of benzodiazepines accounted for an 89% increase in ED visits for the same study period. [5] A Substance Abuse and Mental Health Services Administration (SAMHSA) report in 2013 indicated Oregon had the highest rate of the non-medical use of prescription opioid analgesics for 2010-2011.[6]

The consequences of escalating opioid use in Oregon were reflected in a report from the 2010 Oregon Prescription Opioid Poisoning Workgroup. In 2007 opioid related poisonings accounted for 22.3% of all medication and drug-related hospitalizations in Oregon. Deaths due to prescription opioids in 2008 represented 53% of all deaths due to poisonings by medications and drugs. Methadone poisonings increased 70-fold since 1997 and deaths due to methadone accounted for 33% of the deaths due to poisonings in Oregon in 2008. In 75% of the deaths due to methadone, patients had a history of substance abuse listed in their charts.[7] Other studies have demonstrated that 18-41% of patients using opioids for chronic pain, showed drug abuse behavior.[8]

Policy Summary

In the spring of 2012 the Oregon Department of Medical Assistance Programs (DMAP) implemented a prior authorization (PA) program for all long and short acting opioids analgesics with a total dose exceeding the equivalent of 120mg of morphine sulfate daily(MED).[9–12] Long acting opioid analgesic (LAO) restrictions were implemented April 9, 2012. Short acting opioid analgesics (SAO) restrictions were implemented June 21, 2012. Prior to these changes a PA was required only for non-preferred long acting opioids. The new criteria were approved by the Oregon Medicaid Fee-For-Service (FFS) Pharmacy and Therapeutics Committee and all requests were evaluated in accordance with applicable Oregon Administrative Rules (OAR).[13] Patients treated for cancer-related pain were exempt from the policy (Table A5). Excluded opioid drug products included buprenorphine/naltrexone for substance abuse and combination opioid and acetaminophen products. Key evaluation criteria were: treatment of an Oregon Health Plan (OHP) funded condition, documentation of improvements in both pain control and functional status, a recent (within 90 days of request) urine drug screen (UDS), and the use of a single pharmacy and prescriber for high dose opioids. Temporary authorizations

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were granted for up to 90 days when requested for the purposes of tapering the opioid dose below 120MED, ordering a UDS, or submitting documentation of improvements in pain and functional status.[12,14]

Drug Use Evaluation Goals

- Determine if the policy changed the number of patients receiving high dose opioids
- Determine if prior authorizations were requested, and if so, if they were approved
- Determine if prior authorization requirement caused unintended harms, as identified by changes in health care service utilization

Methods

This retrospective pre/post cohort study evaluated claims from April 9, 2011 until August 9, 2013. Study inclusion and exclusion criteria are summarized in Figure 1. The study included patients with a paid (FFS) pharmacy claim for a qualifying high dose opioid analgesic between January 1, 2012 and April 8,2012 and a denied high dose opioid claim after the policy went into effect (defined as the Index Event). High dose (HD) opioids claims were defined as the total dose exceeding 120mg morphine equivalents daily (MED), as calculated by the strength, quantity and days supply on the paid claim. For short acting opioids, a minimum day supply of 14 days was also required for inclusion. A complete list of qualifying opioid analgesics and morphine equivalents appears in Table A1 of Appendix A. An Index Event (IE) was defined as a FFS claim rejection for a qualifying opioid analgesic with an Explanation of Benefits (EOB) code of either "1056-Prior Authorization Required" or "0030-Drug Quantity Per Day Limit" and without a concurrent EOB of "2017 – Bill Managed Care".

Patients with dual Medicare and Medicaid coverage were excluded, as were all patients with third party insurance (TPL) from one year before until one year after the IE. Patients with more than a 45 day gap in eligibility from one year before until one year after the IE were excluded, except when the loss of eligibility was due to death. The high dose opioid policy did not apply to the treatment of malignant pain, therefore patients with a medical claim indicating a cancer diagnosis (Table A2) with a date of service within 1 year prior to the IE were not subject to the policy and were therefore excluded from the study. Patients with an approved PA for a non preferred opioid analgesic effective on 4/9/2012 were excluded.

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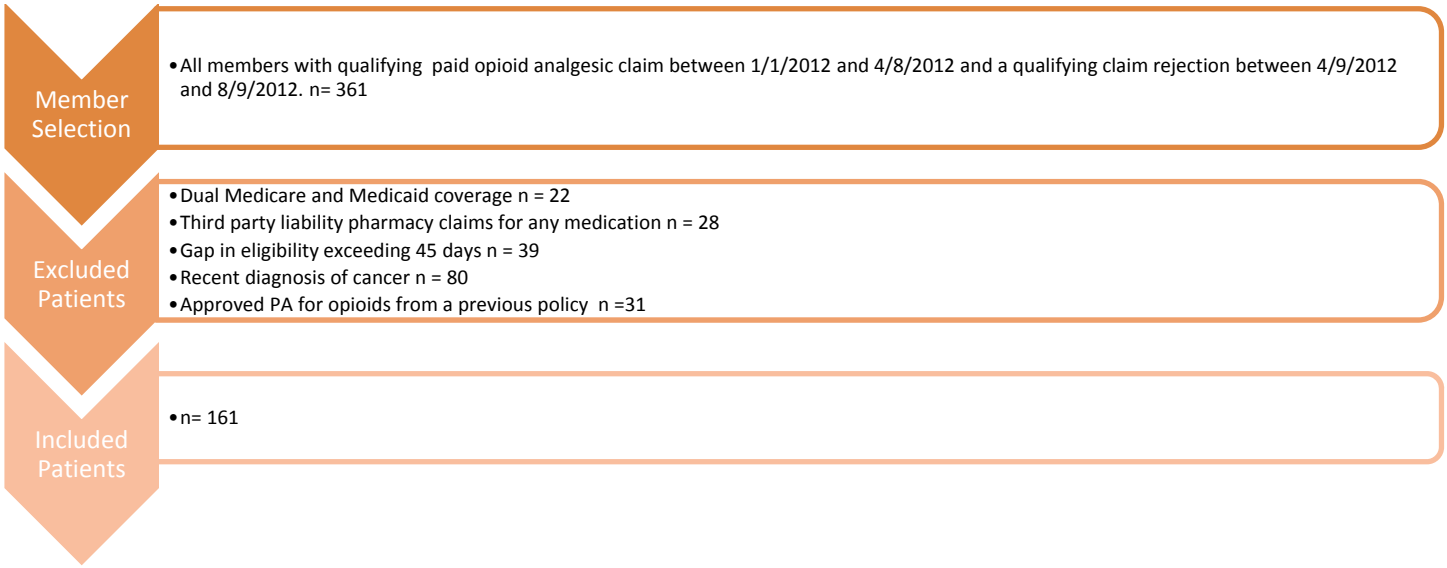

Figure 1 Patient Inclusion Criteria

Baseline Characteristics

Baseline characteristics were collected as potential factors impacting the approval of prior authorizations and health care service utilization (Tables 1-4). Pre-existing pain-related co-morbidities were determined by medical claims within 1 year prior to the IE. International Classification of Diseases, 9th Revision, Clinical Modification (ICD9) codes for each diagnosis group are listed in Table A2. Analgesic therapy, both opioid and non-opioid, were also assessed at baseline. The total opioid dose was calculated as the average MED across all paid opioid claims over the 100 days prior to the IE. Concurrent use of high dose opioids was defined as at least 30 days during which both a long acting and short acting HD opioid were prescribed during the 100 days prior to the IE. Duration of HD therapy was determined looking back at all FFS pharmacy claims for qualifying HD opioid prescriptions. The initiation of HD therapy was defined as the first qualifying HD opioid prescription without a qualifying HD opioid prescription in the preceeeding 45 days. Other analgesics are listed in Table A3 of Appendix A.

Outcomes

Drug therapy disposition (e.g. continued, discontined, etc.) was assessed between the IE plus 100 day to the IE plus 200 days. Patients with at least one qualifying HD opioid analgesic prescription were classified as “High dose opioids continued.” Patients receiving at least one study eligible opioid analgesic (Table A1) not meeting the criteria for high dose or a non-study opioid analgesic (Table A4) were classified as “Continued with any opioid.” Patients with any paid claims for non-opioid analgesics (Table A3) were included in the “Non-opioid analgesic therapy” group. Paid and unpaid claims for any opioid analgesic (Table A1 or A3) were evaluated to identify patients with 3 or more prescribers of opioid analgesics.

Patients potentially paying cash for unapproved high dose opioid prescriptions were identified using a proxy based on denied claims. The proxy was defind as the presence of at least two rejected study eligible opioid analgesic claims between the IE+100 days and the IE+200 days with error codes of either “1056-Prior Authorization Required” or “0030-Drug Quantity Per Day Limit”. Duplicate claims were excluded if a high dose prescription was paid within 4 days for the

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same active agent, the same strength, the same release formulation (immediate or extended). Members with claims meeting these criteria were classified as "Mulitple Unapproved High Dose Opioid Prescriptions."

The final PA disposition was determined at 100 days after the IE. This allowed for temporary authorizations of high dose opioids to occur which allowed patients to safely taper the total daily dose to less than 120 MED or to allow providers to satisfy other PA criteria (e.g. obtain a urine drug screen). These temporary authorizations were provided only upon request by the provider and were typically for no more than 90 days. Patients with PAs submitted for qualifying opioid analgesics after the IE and with approval end days beyond the IE plus 100 days were considered "Approved." Patients with PAs submitted for qualifying opioid analgesics after the IE, but none approved beyond the IE plus 100 days were classified as "Not Approved." All other patients were classified as "Not Requested."

Healthcare service utilization for 1 year prior to the IE and one year after the IE were used to assess potential harms associated with the PA policy. A primary outcome was the composite of all cause hospitalizations, pain related hospitalizations, all cause emergency department (ED) visits, and pain-related ED visits. Hospitalizations and ED encounters were classified as pain related if the primary diagnosis of the encounter was included in table A2.

A secondary composite outcome of substance misuse was identified by outpatient methadone administration, buprenorphine opioid dependence therapy, and opioid overdose. Outpatient methadone administration was identified by medical claims with the procedure code H0020. Outpatient pharmacy claims for methadone were not considered methadone administration for opioid dependence.

Results

Table 1 – Baseline Demographics

Demographics	Members n=161	
	#	%
Age		
0-17	1	1%
25-34	12	7%
35-44	28	17%
45-54	58	36%
55-64	60	37%
65 and Older	2	1%
Gender		
Female	99	61%
Male	62	39%
Race		
Non-White	22	14%
White	139	86%

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Table 2 - Baseline Co-Morbidities

Pain-Related Diagnoses	Members n=161	
	#	%
Pain Conditions		
Bone Disorders	4	2%
Gastrointestinal, hepatic, renal, gynecologic and urologic disorders	53	33%
Gout	4	2%
Headache	37	23%
Multiple Sclerosis	2	1%
Musculoskeletal Disorders	104	65%
Neuropathic Pain Disorders	40	25%
Other Pain Syndromes	78	48%
Rheumatoid Arthritis & Ankylosing spondylitis	10	6%
Soft Tissue Disorders	102	63%
Somatic Pain Disorders	2	1%
Spinal Disorders	121	75%
Substance Abuse / Misuse / Dependence	44	27%
Mental Health Disorders	79	49%

*Individual members may appear in more than one category

Table 3 – Analgesic Drug Therapy – 100 Days Prior to Index Event

Opioid and Related Drug Therapy	Members n=161	
	#	%
Presence of Opioids*		
Fentanyl	21	13%
Hydrocodone/acetaminophen	31	19%
Hydromorphone	11	7%
Methadone	59	37%
Morphine sulfate	57	35%
Oxycodone	63	39%
Oxycodone/acetaminophen	24	15%
Concurrent High Dose LAO and SAO	17	11%
Other Analgesic Therapy		
Antiepileptics	36	22%
NSAIDs	34	21%
Other	35	22%

*Opioids listed in Tables A1 and A4 not appearing in Table 3 had no patients with claims during the 100 days prior to the index event

Table 4 – Dose and Duration of High Dose Opioid Therapy at Baseline

	Mean	Maximum	Minimum
Average Duration of High Dose Opioid of Therapy (Days)	1,077	4,144	13
Average Mg of Morphine Equivalents Daily (MED) for all concurrent opioids	313	1,606	83

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Table 5 - Drug Therapy Disposition by Final Authorization Disposition

	Overall		Final Authorization Disposition					
			Approved		Not Approved		Not Requested	
	#	%	#	%	#	%	#	%
Total	161	100%	59	37%	38	24%	64	40%
Opioid Analgesic Therapy								
High Dose Opioids Continued	43	27%	40	68%	3	8%	0	0%
Continued with low dose opioid	89	55%	15	25%	25	66%	49	77%
No Opioid Therapy	29	18%	4	7%	10	26%	15	23%
Non-Opioid Analgesic Therapy	81	50%	30	51%	18	47%	33	52%
Mulitple Unapproved High Dose Opioid Prescriptions	46	29%	7	12%	11	29%	28	44%

*Drug therapy disposition and prior authorization disposition both assessed at 100 days after the index event

Figure 2 - Unique Members with Paid Claims for High Dose Opioids by Month Relative to the Index Event

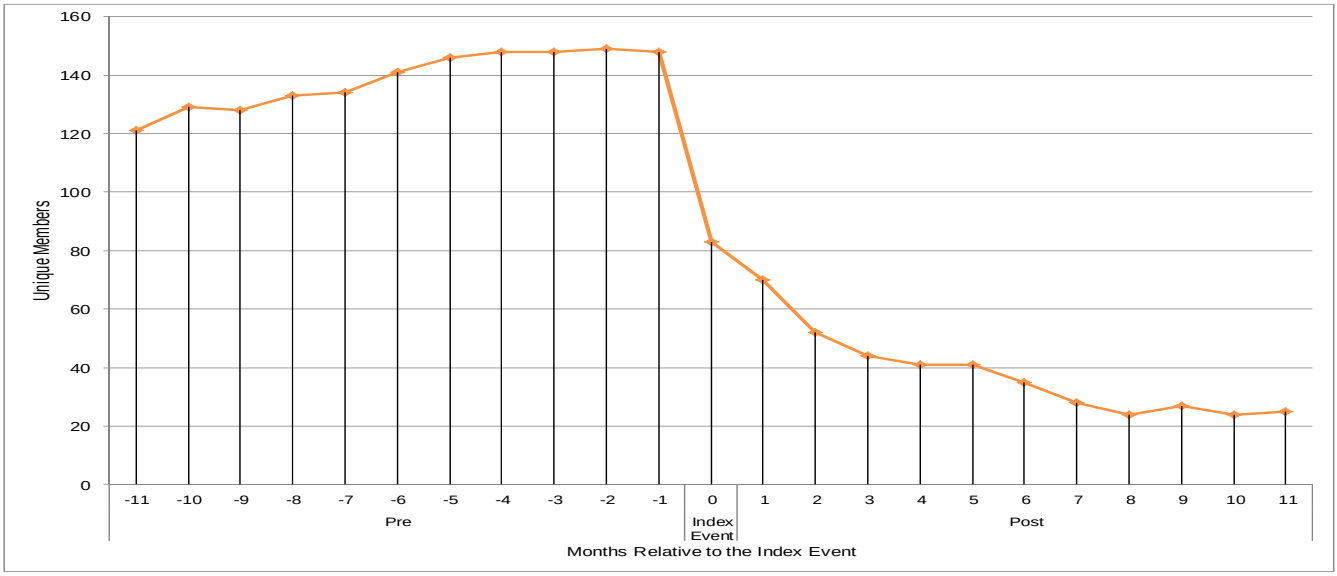

Table 6– Hospital Services

	Overall				Final Authorization Disposition											
					Approved				Not Approved				Not Requested			
	n=161				n=59				n=38				n=64			
	Pre		Post		Pre		Post		Pre		Post		Pre		Post	
	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%
Composite Outcome – All cause hospitalizations and ED visits	70	43%	84	52%	21	36%	23	39%	16	42%	21	55%	33	52%	40	63%
All Cause Hospitalizations	25	16%	30	19%	8	14%	8	14%	6	16%	6	16%	11	17%	16	25%
Pain Related Hospitalizations	4	2%	7	4%	2	3%	1	2%	0	0%	1	3%	2	3%	5	8%
All Cause ED Visits	68	42%	84	52%	20	34%	23	39%	16	42%	21	55%	32	50%	40	63%
Pain Related ED Visits	44	27%	46	29%	13	22%	9	15%	11	29%	14	37%	20	31%	23	36%

The McNemar test found a non-significant (p=0.0769, OR 1.700, CI 0.951 to 3.117) change in all cause hospitalizations. A post hoc analysis found a statistically significant increase in all case ED visits was observed (p=0.045, OR 1.800, CI 1.014 to 3.282). No statistically significant association was found for any of the three prior authorization disposition sub groups for either the composite outcome or all cause ED visits. Outpatient visits per member changed very little (mean 12.31 visits per year before intervention to 12.68 after intervention, median 10.00 both pre and post intervention).

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Post hoc review revealed 41% of members who had a post intervention ED visit also met the proxy measure for paying cash for high dose opioids. This was an increase from 25% in members with pre intervention ED visits. Likewise, 35% members with a post intervention ED visit had a baseline history of substance abuse / misuse /dependence compared to the rates in members with pre-intervention ED visit (18%).

Table 7 Substance Misuse and Dependence

	Overall				Final Authorization Disposition											
					Approved				Not Approved				Not Requested			
	n=161				n=59				n=38				n=64			
	Pre		Post		Pre		Post		Pre		Post		Pre		Post	
	#	%	#	%	#	%	#	%	#	%	#	%	#	%	#	%
Composite Secondary Outcome Substance Misuse and Dependence – Methadone treatment, buprenorphine opioid dependence therapy, and opioid overdose	2	1.2%	5	3.1%	0	0.0%	2	3.4%	0	0.0%	1	2.6%	2	3.1%	2	3.1%
Outpatient Methadone Administration	1	0.6%	2	1.2%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	1.6%	2	3.1%
Buprenorphine opioid dependence therapy	0	0.0%	1	0.6%	0	0.0%	1	1.7%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Opioid Overdose	1	0.6%	2	1.2%	0	0.0%	1	1.7%	0	0.0%	1	2.6%	1	1.6%	0	0.0%

All 5 members meeting the substance misuse and dependence composite outcome after the IE continued on low dose opioid therapy.

There were 4 deaths within one year of the IE. One member was not approved for opioid therapy and the date of death (DOD) was 93 days after the IE. There were no hospital claims on or around the DOD. One day prior to death there was a paid claim for alprazolam 0.25mg tablets quantity dispensed 120 and a denied claim for oxycodone IR 30mg quantity dispensed 120. Of the 3 members with approved therapy, one was in a long term care facility (DOD 97 days after IE), one appears to have died in the hospital possibly due to complications of liver disease (DOD 126 days after IE), and the last had no paid or denied opioid claims within 6 months of the DOD (314 days after IE). The last claim for this final member was from the local fire department, but there are no subsequent hospital claims.

Discussion

There was a clear reduction in the number of members receiving high dose opioids (p = XXXXX). Table 5 shows that only 27% of members continued to have paid pharmacy claims for high dose opioids 100 days after the index event. This 73% reduction in members with paid claims may not reflect actual high dose opioid use. There were 55 members (33%) with multiple denied claims for high dose opioids after 100 days, which was our proxy for continuing therapy by paying cash for prescriptions. This suggests that the actual reduction in patient prescribed high dose opioids may be closer to 40%. It is noteworthy that of the four members who died during the study period, the one with an opioid claim one day prior to death was denied, suggesting therapy had continued despite the PA policy.

A surprising 39% of members did not have PAs requested for their high dose opioid therapy. Of the 97 patients with a PA request, 62% were approved. Of the 64 members without a PA request, 44% had multiple denied claims for high dose opioids after 100 days. This suggests that for some patients and providers, therapy continued despite the policy.

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A non-significant (p=0.0769) increase in the composite outcome for hospital service utilization suggests the policy did not cause harms as measured by the composite outcome, but a ED visits appear to have increased after the policy (p=0.045, OR 1.800, CI 1.014 to 3.282). Interestingly, this increase in ED visits was largely due to non-pain related encounters. These results suggest factors other than painful conditions may be associated with the increase in ED visits due to the policy. The composite outcome for substance misuse and dependence was met by 5 members (3%). Three of these members used either buprenorphine products for opioid dependence or received treatment at a methadone clinic. Currently, there are no policies restricting the use of opioid analgesics in the presence of methadone treatment. Legal restrictions prevent the disclosure of methadone treatment without written consent of the patient. Buprenorphine products used to treat opioid dependence are only approved when no long acting opioids are prescribed, creating a selection bias for no patients receiving buprenorphine therapy at baseline. The clinical and statistical significance of this composite outcome is unclear.

Limitations

The absence of data describing actual prescriptions filled is a major limitation to determining the number of members continuing to receive high dose opioids. Our data clearly shows a reduction in the number of claims paid, while the number of patients with denied high dose opioid claims (33%) suggests that prescribing practices may not have changed. The FFS program does not have access to the Prescription Drug Monitoring Program (PDMP) data. Without access to the PDMP data, it is difficult to determine if the policy changed prescribing practices or simply reduced the number of claims paid for by the program. Although the PMDP cannot disclose patient-level data, they can provide aggregated data matched to a list of patients. A study could be conducted to evaluate high dose opioid therapy in patients who did not have a PA approved using the PDMP data. Such collaboration would provide important public health and policy insights.

The lack of a more robust statistical analysis of the cause of the increase in ED visits represents a signficant limitation of this policy evaluation. A more robust statistical analysis could clarify the factors causing an increase in non-pain related ED visits.

This policy evaluation is subject to the limitations of all claims based retrospective analyses. Claims data is an incomplete and sometimes inaccurate portrait of the true clinical picture.

Recommendations

- Maintain high dose opioid PA policy
- Collaborate with the Prescription Drug Monitoring Program to determine if high dose opioid therapy was continued in patients who did not have a Prior Authorization approved
- Consider a more robust statistical analysis to determine predictors of ED visits

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Appendix A

Table A1 – Study Eligible Opioid Analgesics

Generic Drug Name	Formulation	Morphine Equivalents
CODEINE PHOSPHATE	SOLUTION 15 mg/5 mL	0.45 Per ml
CODEINE SULFATE	SOLUTION 30 mg/5 mL	0.90 Per ml
CODEINE SULFATE	TABLET 15 mg	2.25 Per Unit
CODEINE SULFATE	TABLET 30 mg	4.50 Per Unit
CODEINE SULFATE	TABLET 60 mg	9 Per Unit
FENTANYL	PATCH TD72 100 mcg/hour	360 Per Day
FENTANYL	PATCH TD72 12 mcg/hour	43.20 Per Day
FENTANYL	PATCH TD72 25 mcg/hour	90 Per Day
FENTANYL	PATCH TD72 50 mcg/hour	180 Per Day
FENTANYL	PATCH TD72 75 mcg/hour	270 Per Day
HYDROMORPHONE HCL	CAP24H PEL 12 mg	48 Per Unit
HYDROMORPHONE HCL	CAP24H PEL 16 mg	64 Per Unit
HYDROMORPHONE HCL	CAP24H PEL 24 mg	96 Per Unit
HYDROMORPHONE HCL	CAP24H PEL 32 mg	128 Per Unit
HYDROMORPHONE HCL	LIQUID 1 mg/mL	4 Per ml
HYDROMORPHONE HCL	SUPP.RECT 3 mg	12 Per Unit
HYDROMORPHONE HCL	TAB ER 24H 12 mg	48 Per Unit
HYDROMORPHONE HCL	TAB ER 24H 16 mg	64 Per Unit
HYDROMORPHONE HCL	TAB ER 24H 32 mg	128 Per Unit
HYDROMORPHONE HCL	TAB ER 24H 8 mg	32 Per Unit
HYDROMORPHONE HCL	TABLET 2 mg	8 Per Unit
HYDROMORPHONE HCL	TABLET 3 mg	12 Per Unit
HYDROMORPHONE HCL	TABLET 4 mg	16 Per Unit
HYDROMORPHONE HCL	TABLET 8 mg	32 Per Unit
LEVORPHANOL TARTRATE	TABLET 2 mg	60 Per Unit
MEPERIDINE HCL	SOLUTION 50 mg/5 mL	1 Per ml
MEPERIDINE HCL	TABLET 100 mg	10 Per Unit
MEPERIDINE HCL	TABLET 50 mg	5 Per Unit
METHADONE HCL	ORAL CONC 10 mg/mL	30 Per ml
METHADONE HCL	SOLUTION 10 mg/5 mL	6 Per ml
METHADONE HCL	SOLUTION 5 mg/5 mL	3 Per ml
METHADONE HCL	SYRINGE 10 mg/mL	30 Per ml
METHADONE HCL	SYRINGE 5 mg/5 mL	3 Per ml
METHADONE HCL	TABLET 10 mg	30 Per Unit
METHADONE HCL	TABLET 5 mg	15 Per Unit
METHADONE HCL	TABLET SOL 40 mg	120 Per Unit
MORPHINE SULFATE	CAP ER PEL 10 mg	10 Per Unit
MORPHINE SULFATE	CAP ER PEL 100 mg	100 Per Unit
MORPHINE SULFATE	CAP ER PEL 130 mg	130 Per Unit
MORPHINE SULFATE	CAP ER PEL 150 mg	150 Per Unit
MORPHINE SULFATE	CAP ER PEL 20 mg	20 Per Unit
MORPHINE SULFATE	CAP ER PEL 200 mg	200 Per Unit
MORPHINE SULFATE	CAP ER PEL 30 mg	30 Per Unit
MORPHINE SULFATE	CAP ER PEL 40 mg	40 Per Unit
MORPHINE SULFATE	CAP ER PEL 50 mg	50 Per Unit
MORPHINE SULFATE	CAP ER PEL 60 mg	60 Per Unit
MORPHINE SULFATE	CAP ER PEL 70 mg	70 Per Unit
MORPHINE SULFATE	CAP ER PEL 80 mg	80 Per Unit
MORPHINE SULFATE	CAP24H PEL 100 mg	100 Per Unit
MORPHINE SULFATE	CAP24H PEL 20 mg	20 Per Unit
MORPHINE SULFATE	CAP24H PEL 50 mg	50 Per Unit
MORPHINE SULFATE	CAPSULE 15 mg	15 Per Unit
MORPHINE SULFATE	CAPSULE 30 mg	30 Per Unit
MORPHINE SULFATE	CPMP 24HR 120 mg	120 Per Unit
MORPHINE SULFATE	CPMP 24HR 30 mg	30 Per Unit
MORPHINE SULFATE	CPMP 24HR 45 mg	45 Per Unit
MORPHINE SULFATE	CPMP 24HR 60 mg	60 Per Unit
MORPHINE SULFATE	CPMP 24HR 75 mg	75 Per Unit
MORPHINE SULFATE	CPMP 24HR 90 mg	90 Per Unit
MORPHINE SULFATE	SOLUTION 10 mg/0.5 mL	20 Per ml
MORPHINE SULFATE	SOLUTION 10 mg/5 mL	2 Per ml
MORPHINE SULFATE	SOLUTION 100 mg/5 mL (20 mg/mL)	20 Per ml
MORPHINE SULFATE	SOLUTION 20 mg/5 mL	4 Per ml
MORPHINE SULFATE	SOLUTION 5 mg/0.25 mL	20 Per ml
MORPHINE SULFATE	SUPP.RECT 10 mg	10 Per Unit
MORPHINE SULFATE	SUPP.RECT 20 mg	20 Per Unit
MORPHINE SULFATE	SUPP.RECT 30 mg	30 Per Unit
MORPHINE SULFATE	SUPP.RECT 5 mg	5 Per Unit
MORPHINE SULFATE	SYRINGE 20 mg/mL	20 Per ml
MORPHINE SULFATE	TABLET 15 mg	15 Per Unit
MORPHINE SULFATE	TABLET 30 mg	30 Per Unit
MORPHINE SULFATE	TABLET ER 100 mg	100 Per Unit
MORPHINE SULFATE	TABLET ER 15 mg	15 Per Unit
MORPHINE SULFATE	TABLET ER 200 mg	200 Per Unit
MORPHINE SULFATE	TABLET ER 30 mg	30 Per Unit
MORPHINE SULFATE	TABLET ER 60 mg	60 Per Unit
MORPHINE SULFATE	TABLET SOL 10 mg	10 Per Unit
MORPHINE SULFATE	TABLET SOL 15 mg	15 Per Unit
MORPHINE SULFATE	TABLET SOL 30 mg	30 Per Unit
OXYCODONE HCL	CAPSULE 5 mg	7.50 Per Unit
OXYCODONE HCL	ORAL CONC 20 mg/mL	30 Per ml
OXYCODONE HCL	ORAL CONC 20 mg/mL	30 Per ml
OXYCODONE HCL	SOLUTION 5 mg/5 mL	1.50 Per ml
OXYCODONE HCL	TAB ER 12H 10 mg	15 Per Unit
OXYCODONE HCL	TAB ER 12H 15 mg	22.50 Per Unit
OXYCODONE HCL	TAB ER 12H 160 mg	240 Per Unit
OXYCODONE HCL	TAB ER 12H 20 mg	30 Per Unit
OXYCODONE HCL	TAB ER 12H 30 mg	45 Per Unit
OXYCODONE HCL	TAB ER 12H 40 mg	60 Per Unit
OXYCODONE HCL	TAB ER 12H 60 mg	90 Per Unit
OXYCODONE HCL	TAB ER 12H 80 mg	120 Per Unit
OXYCODONE HCL	TABLET 10 mg	15 Per Unit
OXYCODONE HCL	TABLET 15 mg	22.50 Per Unit
OXYCODONE HCL	TABLET 20 mg	30 Per Unit
OXYCODONE HCL	TABLET 30 mg	45 Per Unit
OXYCODONE HCL	TABLET 5 mg	7.50 Per Unit
OXYCODONE HCL	TABLET ORL 5 mg	7.50 Per Unit
OXYCODONE HCL	TABLET ORL 7.5 mg	11.25 Per Unit
OXYMORPHONE HCL	SUPP.RECT 5 mg	15 Per Unit
OXYMORPHONE HCL	TAB ER 12H 10 mg	30 Per Unit
OXYMORPHONE HCL	TAB ER 12H 15 mg	45 Per Unit
OXYMORPHONE HCL	TAB ER 12H 20 mg	60 Per Unit
OXYMORPHONE HCL	TAB ER 12H 30 mg	90 Per Unit
OXYMORPHONE HCL	TAB ER 12H 40 mg	120 Per Unit
OXYMORPHONE HCL	TAB ER 12H 5 mg	15 Per Unit
OXYMORPHONE HCL	TAB ER 12H 7.5 mg	22.5 Per Unit
OXYMORPHONE HCL	TABLET 10 mg	30 Per Unit
OXYMORPHONE HCL	TABLET 5 mg	15 Per Unit

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Table A2 – Diagnosis Codes

Disorder Category	ICD-9 Code*	ICD-9 Description
Bone Disorders	730	OSTEOMYELITIS PERIOSTITIS&OTH INFS INVLV BONE
Bone Disorders	732	OSTEOCHONDROPATHIES
Bone Disorders	809	ILL-DEFINED FRACTURES OF BONES OF TRUNK
Bone Disorders	810	FRACTURE OF CLAVICLE
Bone Disorders	811	FRACTURE OF SCAPULA
Bone Disorders	812	FRACTURE OF HUMERUS
Bone Disorders	813	FRACTURE OF RADIUS AND ULNA
Bone Disorders	814	FRACTURE OF CARPAL BONE
Bone Disorders	815	FRACTURE OF METACARPAL BONE
Bone Disorders	816	FRACTURE ONE OR MORE PHALANGES OF HAND
Bone Disorders	817	MULTIPLE FRACTURES OF HAND BONES
Bone Disorders	818	ILL-DEFINED FRACTURES OF UPPER LIMB
Bone Disorders	819	MX FX INVOLV BOTH UP LIMBS&UP LIMB W/RIB&STERNUM
Bone Disorders	820	FRACTURE OF NECK OF FEMUR
Bone Disorders	821	FRACTURE OF OTHER AND UNSPECIFIED PARTS OF FEMUR
Bone Disorders	822	FRACTURE OF PATELLA
Bone Disorders	823	FRACTURE OF TIBIA AND FIBULA
Bone Disorders	824	FRACTURE OF ANKLE
Bone Disorders	825	FRACTURE OF ONE OR MORE TARSAL&METATARSAL BONES
Bone Disorders	826	FRACTURE OF ONE OR MORE PHALANGES OF FOOT
Bone Disorders	827	OTHER MULTIPLE&ILL-DEFINED FRACTURES LOWER LIMB
Bone Disorders	828	MULT FX OF LEGS-LEGS W/ARM-LEGS W/RIBS&STERNUM
Bone Disorders	905	LATE EFF MUSCULOSKEL&CONNECTIVE TISSUE INJURIES
Gastrointestinal, hepatic, renal, gynecologic and urologic disorders	250	DIABETES MELLITUS
Gastrointestinal, hepatic, renal, gynecologic and urologic disorders	277	OTHER AND UNSPECIFIED DISORDERS OF METABOLISM
Gastrointestinal, hepatic, renal, gynecologic and urologic disorders	300	ANXIETY DISSOCIATIVE AND SOMATOFORM DISORDERS
Gastrointestinal, hepatic, renal, gynecologic and urologic disorders	453	OTHER VENOUS EMBOLISM AND THROMBOSIS
Gastrointestinal, hepatic, renal, gynecologic and urologic disorders	558	OTHER NONINFECTIOUS GASTROENTERITIS AND COLITIS
Gastrointestinal, hepatic, renal, gynecologic and urologic disorders	571	CHRONIC LIVER DISEASE AND CIRRHOSIS
Gastrointestinal, hepatic, renal, gynecologic and urologic disorders	573	OTHER DISORDERS OF LIVER
Gastrointestinal, hepatic, renal, gynecologic and urologic disorders	574	CHOLELITHIASIS
Gastrointestinal, hepatic, renal, gynecologic and urologic disorders	575	OTHER DISORDERS OF GALLBLADDER
Gastrointestinal, hepatic, renal, gynecologic and urologic disorders	576	OTHER DISORDERS OF BILIARY TRACT
Gastrointestinal, hepatic, renal, gynecologic and urologic disorders	583	NEPHRITIS&NEPHROPATHY NOT SPEC AS ACUTE/CHRONIC
Gastrointestinal, hepatic, renal, gynecologic and urologic disorders	585	CHRONIC KIDNEY DISEASE
Gastrointestinal, hepatic, renal, gynecologic and urologic disorders	614	INFLAM DZ OF OVARY-TUBE-PELVIC TISSUE-PERITONEUM
Gastrointestinal, hepatic, renal, gynecologic and urologic disorders	620	NONINFLAM D/O OVARY FALLOP TUBE&BROAD LIGAMENT
Gastrointestinal, hepatic, renal, gynecologic and urologic disorders	625	PAIN&OTH SYMPTOMS ASSOC W/FEMALE GENITAL ORGANS
Gastrointestinal, hepatic, renal, gynecologic and urologic disorders	751	OTHER CONGENITAL ANOMALIES OF DIGESTIVE SYSTEM
Gastrointestinal, hepatic, renal, gynecologic and urologic disorders	774	OTHER PERINATAL JAUNDICE
Gastrointestinal, hepatic, renal, gynecologic and urologic disorders	777	PERINATAL DISORDERS OF DIGESTIVE SYSTEM
Gastrointestinal, hepatic, renal, gynecologic and urologic disorders	7890	ABDOMINAL PAIN
Gastrointestinal, hepatic, renal, gynecologic and urologic disorders	996	COMPLICATIONS PECULIAR CERTAIN SPECIFIED PROC
Gout	274	GOUT
Gout	712	CRYSTAL ARTHROPATHIES
Headache	30781	TENSION HEADACHE
Headache	339	OTHER HEADACHE SYNDROMES
Headache	346	MIGRAINE
Headache	7840	HEADACHE
Multiple Sclerosis	334	SPINOCEREBELLAR DISEASE
Multiple Sclerosis	340	MULTIPLE SCLEROSIS
Musculoskeletal Disorders	272	DISORDERS OF LIPOID METABOLISM
Musculoskeletal Disorders	355	MONONEURITIS OF LOWER LIMB AND UNSPECIFIED SITE
Musculoskeletal Disorders	524	DENTOFACIAL ANOMALIES INCLUDING MALOCCLUSION
Musculoskeletal Disorders	713	ARTHRPATH W/OTH DISORDERS CLASSIFIED ELSEWHERE

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Disorder Category	ICD-9 Code*	ICD-9 Description
Musculoskeletal Disorders	715	OSTEOARTHROSIS AND ALLIED DISORDERS
Musculoskeletal Disorders	716	OTHER AND UNSPECIFIED ARTHROPATHIES
Musculoskeletal Disorders	717	INTERNAL DERANGEMENT OF KNEE
Musculoskeletal Disorders	718	OTHER DERANGEMENT OF JOINT
Musculoskeletal Disorders	719	OTHER AND UNSPECIFIED DISORDERS OF JOINT
Musculoskeletal Disorders	726	PERIPHERAL ENTHESOPATHIES AND ALLIED SYNDROMES
Musculoskeletal Disorders	727	OTHER DISORDERS OF SYNOVIUM TENDON AND BURSA
Musculoskeletal Disorders	728	DISORDERS OF MUSCLE LIGAMENT AND FASCIA
Musculoskeletal Disorders	731	OSTEITIS DEFORMANS & OSTEOPATHIES W/OTH D/O CE
Musculoskeletal Disorders	733	OTHER DISORDERS OF BONE AND CARTILAGE
Musculoskeletal Disorders	736	OTHER ACQUIRED DEFORMITIES OF LIMBS
Musculoskeletal Disorders	748	CONGENITAL ANOMALIES OF RESPIRATORY SYSTEM
Musculoskeletal Disorders	755	OTHER CONGENITAL ANOMALIES OF LIMBS
Musculoskeletal Disorders	756	OTHER CONGENITAL MUSCULOSKELETAL ANOMALIES
Musculoskeletal Disorders	781	SYMPTOMS INVLV NERVOUS&MUSCULOSKELETAL SYSTEMS
Musculoskeletal Disorders	830	DISLOCATION OF JAW
Musculoskeletal Disorders	831	DISLOCATION OF SHOULDER
Musculoskeletal Disorders	832	DISLOCATION OF ELBOW
Musculoskeletal Disorders	833	DISLOCATION OF WRIST
Musculoskeletal Disorders	834	DISLOCATION OF FINGER
Musculoskeletal Disorders	835	DISLOCATION OF HIP
Musculoskeletal Disorders	836	DISLOCATION OF KNEE
Musculoskeletal Disorders	837	DISLOCATION OF ANKLE
Musculoskeletal Disorders	838	DISLOCATION OF FOOT
Musculoskeletal Disorders	839	OTHER MULTIPLE AND ILL-DEFINED DISLOCATIONS
Musculoskeletal Disorders	840	SPRAINS AND STRAINS OF SHOULDER AND UPPER ARM
Musculoskeletal Disorders	841	SPRAINS AND STRAINS OF ELBOW AND FOREARM
Musculoskeletal Disorders	842	SPRAINS AND STRAINS OF WRIST AND HAND
Musculoskeletal Disorders	843	SPRAINS AND STRAINS OF HIP AND THIGH
Musculoskeletal Disorders	844	SPRAINS AND STRAINS OF KNEE AND LEG
Musculoskeletal Disorders	845	SPRAINS AND STRAINS OF ANKLE AND FOOT
Musculoskeletal Disorders	846	SPRAINS AND STRAINS OF SACROILIAC REGION
Musculoskeletal Disorders	847	SPRAINS&STRAINS OTHER&UNSPECIFIED PARTS BACK
Musculoskeletal Disorders	848	OTHER AND ILL-DEFINED SPRAINS AND STRAINS
Neuropathic Pain Disorders	053	HERPES ZOSTER
Neuropathic Pain Disorders	350	TRIGEMINAL NERVE DISORDERS
Neuropathic Pain Disorders	352	DISORDERS OF OTHER CRANIAL NERVES
Neuropathic Pain Disorders	353	NERVE ROOT AND PLEXUS DISORDERS
Neuropathic Pain Disorders	354	MONONEURITIS UPPER LIMB&MONONEURITIS MULTIPLEX
Neuropathic Pain Disorders	357	INFLAMMATORY AND TOXIC NEUROPATHY
Neuropathic Pain Disorders	443	OTHER PERIPHERAL VASCULAR DISEASE
Neuropathic Pain Disorders	952	SPINAL CORD INJURY W/O EVIDENCE SPINAL BN INJURY
Neuropathic Pain Disorders	953	INJURY TO NERVE ROOTS AND SPINAL PLEXUS
Neuropathic Pain Disorders	954	INJURY OTH NERVE TRUNK EXCLD SHLDR&PELV GIRDLS
Neuropathic Pain Disorders	955	INJURY PERIPH NERVE SHOULDER GIRDL&UPPER LIMB
Neuropathic Pain Disorders	956	INJURY PERIPHERAL NERVE PELVIC GIRDLE&LOWER LIMB
Neuropathic Pain Disorders	957	INJURY TO OTHER AND UNSPECIFIED NERVES
Neuropathic Pain Disorders	958	CERTAIN EARLY COMPLICATIONS OF TRAUMA
Neuropathic Pain Disorders	959	INJURY, OTHER AND UNSPECIFIED
Other Pain Syndromes	338	PAIN NOT ELSEWHERE CLASSIFIED
Rheumatoid Arthritis & Ankylosing spondylitis	714	RA AND OTHER INFLAMMATORY POLYARTHROPATHIES
Rheumatoid Arthritis & Ankylosing spondylitis	720	ANKYLOSING SPONDYLITIS&INFLAM SPONDYLOPATHIES
Soft Tissue Disorders	680	CARBUNCLE AND FURUNCLE
Soft Tissue Disorders	681	CELLULITIS AND ABSCESS OF FINGER AND TOE
Soft Tissue Disorders	682	OTHER CELLULITIS AND ABSCESS
Soft Tissue Disorders	684	IMPETIGO
Soft Tissue Disorders	685	PILONIDAL CYST
Soft Tissue Disorders	686	OTHER LOCAL INFECTION SKIN&SUBCUTANEOUS TISSUE
Soft Tissue Disorders	703	DISEASES OF NAIL

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Disorder Category	ICD-9 Code*	ICD-9 Description
Soft Tissue Disorders	707	CHRONIC ULCER OF SKIN
Soft Tissue Disorders	709	OTHER DISORDERS OF SKIN AND SUBCUTANEOUS TISSUE
Soft Tissue Disorders	710	DIFFUSE DISEASES OF CONNECTIVE TISSUE
Soft Tissue Disorders	725	POLYMYALGIA RHEUMATICA
Soft Tissue Disorders	729	OTHER DISORDERS OF SOFT TISSUES
Soft Tissue Disorders	782	SYMPTOMS INVOLVING SKIN&OTH INTEGUMENTARY TISSUE
Soft Tissue Disorders	870	OPEN WOUND OF OCULAR ADNEXA
Soft Tissue Disorders	872	OPEN WOUND OF EAR
Soft Tissue Disorders	873	OTHER OPEN WOUND OF HEAD
Soft Tissue Disorders	875	OPEN WOUND OF CHEST
Soft Tissue Disorders	876	OPEN WOUND OF BACK
Soft Tissue Disorders	877	OPEN WOUND OF BUTTOCK
Soft Tissue Disorders	878	OPEN WOUND GENITAL ORGANS INCL TRAUMATIC AMP
Soft Tissue Disorders	879	OPEN WOUND OTHER&UNSPECIFIED SITES EXCEPT LIMBS
Soft Tissue Disorders	880	OPEN WOUND OF SHOULDER AND UPPER ARM
Soft Tissue Disorders	881	OPEN WOUND OF ELBOW FOREARM AND WRIST
Soft Tissue Disorders	882	OPEN WOUND OF HAND EXCEPT FINGER ALONE
Soft Tissue Disorders	883	OPEN WOUND OF FINGER
Soft Tissue Disorders	884	MULTIPLE&UNSPECIFIED OPEN WOUND OF UPPER LIMB
Soft Tissue Disorders	890	OPEN WOUND OF HIP AND THIGH
Soft Tissue Disorders	891	OPEN WOUND OF KNEE, LEG , AND ANKLE
Soft Tissue Disorders	892	OPEN WOUND OF FOOT EXCEPT TOE ALONE
Soft Tissue Disorders	893	OPEN WOUND OF TOE
Soft Tissue Disorders	894	MULTIPLE&UNSPECIFIED OPEN WOUND OF LOWER LIMB
Soft Tissue Disorders	895	TRAUMATIC AMPUTATION OF TOE
Soft Tissue Disorders	910	SUPERFICIAL INJURY OF FACE NECK&SCALP EXCEPT EYE
Soft Tissue Disorders	911	SUPERFICIAL INJURY OF TRUNK
Soft Tissue Disorders	912	SUPERFICIAL INJURY OF SHOULDER AND UPPER ARM
Soft Tissue Disorders	913	SUPERFICIAL INJURY OF ELBOW FOREARM AND WRIST
Soft Tissue Disorders	914	SUPERFICIAL INJURY OF HAND EXCEPT FINGER ALONE
Soft Tissue Disorders	915	SUPERFICIAL INJURY OF FINGER
Soft Tissue Disorders	916	SUPERFICIAL INJURY OF HIP THIGH LEG AND ANKLE
Soft Tissue Disorders	917	SUPERFICIAL INJURY OF FOOT AND TOE
Soft Tissue Disorders	919	SUPERFICIAL INJURY OTHER MULTIPLE&UNSPEC SITES
Soft Tissue Disorders	920	CONTUSION OF FACE, SCALP, AND NECK EXCEPT EYE(S)
Soft Tissue Disorders	921	CONTUSION OF EYE AND ADNEXA
Soft Tissue Disorders	922	CONTUSION OF TRUNK
Soft Tissue Disorders	923	CONTUSION OF UPPER LIMB
Soft Tissue Disorders	924	CONTUSION LOWER LIMB&OF OTHER&UNSPECIFIED SITES
Soft Tissue Disorders	940	BURN CONFINED TO EYE AND ADNEXA
Soft Tissue Disorders	941	BURN OF FACE, HEAD, AND NECK
Soft Tissue Disorders	942	BURN OF TRUNK
Soft Tissue Disorders	943	BURN OF UPPER LIMB EXCEPT WRIST AND HAND
Soft Tissue Disorders	944	BURN OF WRIST AND HAND
Soft Tissue Disorders	945	BURN OF LOWER LIMB
Soft Tissue Disorders	946	BURNS OF MULTIPLE SPECIFIED SITES
Soft Tissue Disorders	947	BURN OF INTERNAL ORGANS
Soft Tissue Disorders	949	BURN, UNSPECIFIED SITE
Somatic Pain Disorders	306	PHYSIOLOGICAL MALFUNCTION ARISE FROM MENTAL FCT
Somatic Pain Disorders	307	SPECIAL SYMPTOMS OR SYNDROMES NEC
Spinal Disorders	336	OTHER DISEASES OF SPINAL CORD
Spinal Disorders	344	OTHER PARALYTIC SYNDROMES
Spinal Disorders	349	OTHER&UNSPECIFIED DISORDERS THE NERVOUS SYSTEM
Spinal Disorders	721	SPONDYLOSIS AND ALLIED DISORDERS
Spinal Disorders	722	INTERVERTEBRAL DISC DISORDERS
Spinal Disorders	723	OTHER DISORDERS OF CERVICAL REGION
Spinal Disorders	724	OTHER AND UNSPECIFIED DISORDERS OF BACK
Spinal Disorders	737	CURVATURE OF SPINE
Spinal Disorders	738	OTHER ACQUIRED MUSCULOSKELETAL DEFORMITY

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Disorder Category	ICD-9 Code*	ICD-9 Description
Spinal Disorders	739	NONALLOPATHIC LESIONS NOT ELSEWHERE CLASSIFIED
Spinal Disorders	742	OTHER CONGENITAL ANOMALIES OF NERVOUS SYSTEM
Spinal Disorders	754	CERTAIN CONGENITAL MUSCULOSKELETAL DEFORMITIES
Spinal Disorders	805	FX VERT COLUMN W/O MENTION SPINAL CORD INJURY
Spinal Disorders	806	FRACTURE VERTEBRAL COLUMN W/SPINAL CORD INJURY

*Includes all child codes

Table A3 – Non-Opioid Analgesics

Generic Drug Name	Type
AMITRIPTYLINE HCL	Other
BROMFENAC SODIUM	NSAID
CELECOXIB	NSAID
DICLOFENAC POTASSIUM	NSAID
DICLOFENAC SODIUM	NSAID
DIFLUNISAL	NSAID
DULOXETINE HCL	Other
ETODOLAC	NSAID
FENOPROFEN CALCIUM	NSAID
FLURBIPROFEN	NSAID
GABAPENTIN	Antiepileptic
IBUPROFEN	NSAID
INDOMETHACIN	NSAID
KETOPROFEN	NSAID
KETOROLAC TROMETHAMINE	NSAID
MECLOFENAMATE SODIUM	NSAID
MEFENAMIC ACID	NSAID
MELOXICAM	NSAID
NABUMETONE	NSAID
NAPROXEN	NSAID
NAPROXEN SODIUM	NSAID
OXAPROZIN	NSAID
PIROXICAM	NSAID
PREGABALIN	Antiepileptic
ROFECOXIB	NSAID
SALSALATE	NSAID
SULINDAC	NSAID
TOLMETIN SODIUM	NSAID
TRAMADOL HCL	Other
TRAMADOL HCL/ACETAMINOPHEN	Other
VALDECOXIB	NSAID

NSAID = Non-Steroidal Anti Inflammatory Drug

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Table A4 –Non-Study Opioid Analgesics

Generic Drug Name
ACETAMINOPHEN WITH CODEINE
ALFENTANIL HCL
ASPIRIN/CODEINE PHOSPHATE
BUPRENORPHINE
BUPRENORPHINE HCL*
BUTALBIT/ACETAMIN/CAFF/CODEINE
BUTORPHANOL TARTRATE
COD/ASA/SALICYLMD/ACETAMIN/CAF
CODEINE/BUTALBITAL/ASA/CAFFEIN
CODEINE/CARISOPRODOL/ASPIRIN
DHCODEINE BT/ACETAMINOPHN/CAFF
DIHYDROCODEINE/ASPIRIN/CAFFEIN
FENTANYL CITRATE
FENTANYL CITRATE-0.9 % NACL/PF
FENTANYL CITRATE/D5W/PF
FENTANYL CITRATE/DROPERIDOL
FENTANYL CITRATE/PF
FENTANYL/BUPIVACAINE/NS/PF
FENTANYL/ROPIVACAINE/NS/PF
HYDROCODONE BITARTRATE/ASPIRIN
HYDROCODONE/ACETAM/DIET.SUP.11
HYDROCODONE/ACETAMINOPHEN
HYDROCODONE/IBUPROFEN
HYDROMORPHONE HCL IN 0.9% NACL

Generic Drug Name
HYDROMORPHONE HCL IN D5W/PF
HYDROMORPHONE HCL/0.9% NACL/PF
HYDROMORPHONE HCL/PF
HYDROMORPHONE/BUPIV/0.9NACL/PF
IBUPROFEN/OXYCODONE HCL
LEVOMETHADYL ACETATE HCL
MEPERIDINE HCL IN 0.9 % NACL
MEPERIDINE HCL/PF
MEPERIDINE HCL/PROMETH HCL
METHADONE HCL IN 0.9 % NACL
MORPHINE IN NACL, ISO-OSM/PF
MORPHINE SULFATE IN 0.9 % NACL
MORPHINE SULFATE LIPOSOMAL/PF
MORPHINE SULFATE/0.9% NACL/PF
MORPHINE SULFATE/D5W
MORPHINE SULFATE/D5W/PF
MORPHINE SULFATE/NALTREXONE
MORPHINE SULFATE/PF
NALBUPHINE HCL
OPIUM/ASPIRIN/CAFFEINE
OPIUM/ASPIRIN/CAFFEINE/CAMPHOR
OPIUM/BELLADONNA ALKALOIDS
OXYCODONE HCL/ACETAMINOPHEN
OXYCODONE HCL/ASPIRIN

Generic Drug Name
OXYCODONE HCL/OXYCODON TER/ASA
OXYCODONE/ASPIRIN
PENTAZOCINE HCL/ACETAMINOPHEN
PENTAZOCINE HCL/ASPIRIN
PENTAZOCINE HCL/NALOXONE HCL
PENTAZOCINE LACTATE
PROPOXYPHENE HCL
PROPOXYPHENE HCL/ACETAMINOPHEN
PROPOXYPHENE NAP/ACETAMINOPHEN
PROPOXYPHENE NAPSYLATE
PROPOXYPHENE/ASPIRIN/CAFFEINE
REMIFENTANIL HCL
REMIFENTANIL IN 0.9 % NACL/PF
SUFENTANIL CITRATE
SUFENTANIL CITRATE/PF
SUFENTANIL/BUPIVACAINE/NS/PF
TAPENTADOL HCL

*Buprenorphine HCL sublingual tablets are excluded

Table A5 – Other Diagnosis Codes

Disorder Category	ICD-9 Code*	ICD-9 Description
Cancer	140	MALIGNANT NEOPLASM OF LIP
Cancer	141	MALIGNANT NEOPLASM OF TONGUE
Cancer	142	MALIGNANT NEOPLASM OF MAJOR SALIVARY GLANDS
Cancer	143	MALIGNANT NEOPLASM OF GUM
Cancer	144	MALIGNANT NEOPLASM OF FLOOR OF MOUTH
Cancer	145	MALIGNANT NEOPLASM OTHER&UNSPECIFIED PARTS MOUTH
Cancer	146	MALIGNANT NEOPLASM OF OROPHARYNX
Cancer	147	MALIGNANT NEOPLASM OF NASOPHARYNX
Cancer	148	MALIGNANT NEOPLASM OF HYPOPHARYNX
Cancer	149	MAL NEOPLASM-OTH SITES-LIP-ORAL CAVITY-PHARYNX
Cancer	150	MALIGNANT NEOPLASM OF ESOPHAGUS
Cancer	151	MALIGNANT NEOPLASM OF STOMACH
Cancer	152	MALIG NEOPLASM SMALL INTESTINE INCL DUODENUM
Cancer	153	MALIGNANT NEOPLASM OF COLON
Cancer	154	MALIG NEOPLASM RECTUM RECTOSIGMOID JUNCTION&ANUS
Cancer	155	MALIGNANT NEOPLASM OF LIVER AND INTRAHEPATIC BDS
Cancer	156	MALIGNANT NEOPLASM GALLBLADDER&EXTRAHEPATIC BDS
Cancer	157	MALIGNANT NEOPLASM OF PANCREAS
Cancer	158	MALIGNANT NEOPLASM OF RETROPERITONEUM&PERITONEUM
Cancer	159	MALIG NEO DIGES ORGANS&PANCREAS-OTH SITES
Cancer	160	MALIG NEOPLSM NASL CAVITIES MID EAR&ACSS SINUSES
Cancer	161	MALIGNANT NEOPLASM OF LARYNX
Cancer	162	MALIGNANT NEOPLASM OF TRACHEA BRONCHUS AND LUNG
Cancer	163	MALIGNANT NEOPLASM OF PLEURA
Cancer	164	MALIGNANT NEOPLASM OF THYMUS HEART&MEDIASTINUM
Cancer	165	MAL NEO-OTH ILL-DEF RESP SYS-INTRATHORACIC
Cancer	170	MALIGNANT NEOPLASM OF BONE&ARTICULAR CARTILAGE

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Disorder Category	ICD-9 Code*	ICD-9 Description
Cancer	171	MALIGNANT NEOPLASM CONNECTIVE&OTHER SOFT TISSUE
Cancer	172	MALIGNANT MELANOMA OF SKIN
Cancer	173	OTHER MALIGNANT NEOPLASM OF SKIN
Cancer	174	MALIGNANT NEOPLASM OF FEMALE BREAST
Cancer	175	MALIGNANT NEOPLASM OF MALE BREAST
Cancer	176	KAPOSIS SARCOMA
Cancer	179	MALIGNANT NEOPLASM OF UTERUS, PART UNSPECIFIED
Cancer	180	MALIGNANT NEOPLASM OF CERVIX UTERI
Cancer	181	MALIGNANT NEOPLASM OF PLACENTA
Cancer	182	MALIGNANT NEOPLASM OF BODY OF UTERUS
Cancer	183	MALIGNANT NEOPLASM OF OVARY&OTHER UTERINE ADNEXA
Cancer	184	MALIG NEOPLASM OTH&UNSPEC FEMALE GENITAL ORGANS
Cancer	185	MALIGNANT NEOPLASM OF PROSTATE
Cancer	186	MALIGNANT NEOPLASM OF TESTIS
Cancer	187	MALIG NEOPLASM PENIS&OTHER MALE GENITAL ORGANS
Cancer	188	MALIGNANT NEOPLASM OF BLADDER
Cancer	189	MALIG NEOPLASM KIDNEY&OTH&UNSPEC URINARY ORGANS
Cancer	190	MALIGNANT NEOPLASM OF EYE
Cancer	191	MALIGNANT NEOPLASM OF BRAIN
Cancer	192	MALIG NEOPLASM OTHER&UNSPEC PARTS NERVOUS SYSTEM
Cancer	193	MALIGNANT NEOPLASM OF THYROID GLAND
Cancer	194	MALIG NEOPLASM OTH ENDOCRN GLANDS&RELATED STRCT
Cancer	195	MALIGNANT NEOPLASM OF OTHER&ILL-DEFINED SITES
Cancer	196	SEC&UNSPECIFIED MALIGNANT NEOPLASM LYMPH NODES
Cancer	197	SEC MALIG NEOPLASM RESPIRATORY&DIGESTIVE SYSTEMS
Cancer	198	SEC MALIGNANT NEOPLASM OF OTHER SPECIFIED SITES
Cancer	199	MALIGNANT NEOPLASM WITHOUT SPECIFICATION OF SITE
Cancer	200	LYMPH & RETICSRC & OTH SPEC LYMPH MALIG TUMORS
Cancer	201	HODGKINS DISEASE
Cancer	202	OTH MALIG NEOPLASMS LYMPHOID&HISTIOCYTIC TISSUE
Cancer	203	MULTIPLE MYELOMA&IMMUNOPROLIFERATIVE NEOPLASMS
Cancer	204	LYMPHOID LEUKEMIA
Cancer	205	MYELOID LEUKEMIA
Cancer	206	MONOCYTIC LEUKEMIA
Cancer	207	OTHER SPECIFIED LEUKEMIA
Cancer	208	LEUKEMIA OF UNSPECIFIED CELL TYPE
Cancer	209	NEUROENDOCRINE TUMORS
Cancer	2090	MALIGNANT CARCINOID TUMORS OF SMALL INTESTINE
Cancer	2091	MALIG CARCINOID TUMORS APPENDIX LG INTEST RECTUM
Cancer	2092	MALIGNANT CARCINOID TUMORS OF OTHER & UNS SITES
Cancer	2093	MALIG POORLY DIFFERENTIATED NEUROENDOCRIN TUMORS
Cancer	2097	SECONDARY NEUROENDOCRINE TUMORS
Cancer	3383	NEOPLASM RELATED PAIN (ACUTE) (CHRONIC)

*Includes all child codes

Table A6 – Health Outcome Codes

Description	Codes
Hospitalizations	Claim Type = I
ED Visits	Procedure Codes 99281-99285, 99288 OR Revenue Center Codes 0450-0459 or 0981
Outpatient methadone administration	CPT Code H0020
Buprenorphine opioid dependence therapy	BUPRENORPHINE HCL TAB SUBL BUPRENORPHINE HCL/NALOXONE HCL FILM BUPRENORPHINE HCL/NALOXONE HCL TAB SUBL
Opioid Overdose	ICD9 Codes 9650, 96500, 96501, 96502, 96509, E8500, E8501, E8502, E9500
Outpatient Visits	CPT Codes 90000, 90010, 90015, 90017, 90020, 90030, 90040, 90050, 90060, 90070, 90080, 90804, 90805, 90806, 90807, 90808, 90809, 90810, 90812, 90814, 97700, 97701, 99056, 99058, 99060, 99201, 99202, 99203, 99204, 99205, 99211, 99212, 99213, 99214, 99215, 99241, 99242, 99243, 99244, 99245, 99354, 99355, D9430, D9440, FPS18, M0005, M0007, M0008, M0009, Q0044, TAS01, TAS02, TAS03, TAS04