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Drug Class Update: Laxatives for Chronic Constipation

Date of Review: April 2020

Date of Last Review: July 2017
Dates of Literature Search: 1/1/2017 – 12/17/2019

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

Purpose for Class Update:
The drugs for constipation class will be reviewed to determine if there is any relevant, updated evidence to be incorporated into the recommendations provided to the Oregon Health Plan (OHP). Evidence identified since the July 2017 review will be included.

Research Questions:

- Is there evidence for differences in clinical efficacy or effectiveness for linaclotide, lubiprostone, alvimopan, methylnaltrexone, naloxegol, naldemedine, plecanatide, prucalopride, tegaserod, or tenapanor over traditional laxatives used to manage constipation?
- Is there evidence for differences in safety for linaclotide, lubiprostone, alvimopan, methylnaltrexone, naloxegol, naldemedine, plecanatide, prucalopride, tegaserod, or tenapanor over traditional laxatives used to manage constipation?
- Are there subgroups of patients based on demographics (e.g., 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?

Conclusions:

- Three systematic reviews[1-3] and 3 clinical guidelines[4-6] were published since the last laxative class update was presented to the P and T Committee.
- A 2018 Cochrane systematic review updated a 2012 publication which evaluated safety and efficacy of osmotic and stimulant laxatives in children with chronic idiopathic constipation (CIC).[1] The pooled analyses from 11 randomized controlled trials (RCT) suggest that polyethylene glycol (PEG) preparations may be superior to placebo, lactulose and milk of magnesia for childhood constipation.[1] However, the overall quality of the evidence for the primary outcome (number of stools per week) was low or very low due to sparse, heterogeneous data, and high risk of bias from the studies in the pooled analyses.[1] There is no evidence to demonstrate the superiority of lactulose in pediatric CIC when compared to the other agents studied.[1]
- A 2018 Cochrane update evaluated safety and efficacy for mu-opioid antagonists (MOAs) for alleviating opioid-induced constipation (OIC) in adults with cancer or receiving palliative care.[2] Moderate-quality evidence from one trial suggests naldemedine improves bowel function in patients with OIC and cancer in whom conventional laxatives have failed, but increases the risk of adverse events.[2] Moderate-quality evidence from 2 trials suggests methylnaltrexone improves bowel function in people receiving palliative care with OIC, and low-quality evidence shows that it does not increase adverse events.[2]

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- A high-quality systematic review published in 2018 evaluated the efficacy of medications approved to treat OIC.[3] Twenty-six placebo-controlled RCTs evaluating methylnaltrexone, naloxone, naloxegol, alvimopan, prucalopride, lubiprostone, and naldemedine met inclusion criteria.[3] The most common primary outcome was 3 or more bowel movements (BMs) per week over the trial period.[3] In the meta-analysis, 51% of subjects who received an OIC treatment (MOAs, lubiprostone, or prucalopride) had a favorable response to therapy, compared with 33% of individuals randomized to placebo, for an overall number needed to treat (NNT) of 5.[3] The overall relative risk for failure to respond to therapy was significantly lower for those who received drug versus placebo [Relative Risk (RR) 0.70, 95% Confidence Interval (CI) 0.64 to 0.75].[3] Individually, the NNT for lubiprostone was 15, naloxegol was 7, methylnaltrexone and naloxone was 4, and naldemedine was 5.[3] Compared to other medications, lubiprostone was the least efficacious in treating OIC.[3] After pooling all treatments, adverse effects were significantly higher in those who received drug versus placebo, with a number needed to harm (NNH) of 20.[3] A limitation of this systematic review was the significant heterogeneity across 26 studies, likely owing to the inclusion of multiple drugs, varying baseline opioid use, and different subject populations (cancer versus non–cancer-related pain).[3]
- The 2018 American College of Gastroenterology (ACG) engaged a panel of gastroenterologists to update a 2014 monograph for treatment of irritable bowel syndrome (IBS).[4] Moderate-quality evidence suggests psyllium should be recommended as first-line therapy for overall symptom improvement in patients with IBS with constipation (IBC-C).[4] Strong recommendations based on moderate- to high-quality evidence suggest linaclotide, plecanatide, and lubiprostone improve symptoms among patients with IBS-C compared with placebo.[4]
- The 2019 Canadian Association of Gastroenterology (CAG) clinical practice guideline for management of IBS strongly recommended soluble fiber supplementation as an initial, low-cost, safe treatment option that is acceptable to patients and has moderate-quality evidence that it improves IBS-C symptoms.[5] High-quality evidence supports a strong recommendation for the use of linaclotide to improve IBS-C symptoms.[5] In light of the fact that lubiprostone treatment is expensive, and there are no comparative studies to evaluate whether it is more effective than other less expensive treatments, the consensus group made a conditional recommendation in favor of using lubiprostone in IBS-C patients based on moderate-quality evidence.[5] Plecanatide was not included in the CAG document because it is not commercially available in Canada.
- Recommendations of the American Gastroenterological Association (AGA) on the medical management of OIC were published in 2019.[6] Due to insufficient evidence, AGA does not recommend lubiprostone or prucalopride in patients with OIC. Strong recommendations based on moderate- to high-quality evidence are summarized below:
    - In patients with OIC, the AGA recommends use of laxatives as first-line agents (Quality of evidence: High).[6]
    - In patients with laxative refractory OIC, the AGA recommends naldemedine (Quality of evidence: High).[6]
    - In patients with laxative refractory OIC, the AGA recommends naloxegol (Quality of evidence: Moderate).[6]
- 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.

Recommendations:

- Designate prucalopride, tegaserod, and tenapanor as non-preferred on the Practitioner-Managed Prescription Drug Plan (PMPDP) to assure use in OHP-funded conditions.
- Revise laxatives for constipation prior authorization (PA) criteria to include prucalopride, tegaserod, and tenapanor.
- Review drug costs in the executive session.

Summary of Prior Reviews and Current Policy

Drugs for constipation were last reviewed by the P and T Committee at the July 2017 meeting when abbreviated drug reviews for plecanatide and naldemedine were presented. Constipation, IBS-C, and OIC are not currently funded under the Oregon Health Plan Prioritized List of Health Services.[2] Funding for drugs that treat constipation is dependent on whether constipation adversely effects, or is secondary to, an underlying medical condition covered by the prioritized list. Therefore, prior authorization criteria were implemented to help guide decision making for nonpreferred drug utilization in funded conditions. Nonpreferred drugs include: linaclotide, methylnaltrexone, naloxegol, naldemedine, alvimopan, lubiprostone, and plecanatide. Preferred laxatives on the PDL include: PEG, docusate, senna, magnesium hydroxide, calcium polycarbophil, bisacodyl, lactulose, psyllium, magnesium citrate, and methylcellulose. One hundred percent of OHP Fee-for-Service (FFS) utilization is for the preferred laxatives. Prior authorization criteria are included in **Appendix 3**.

Background:

Functional bowel disorders are a spectrum of chronic gastrointestinal (GI) disorders characterized by predominant symptoms or signs of abdominal pain, bloating, distention, or bowel habit abnormalities (e.g., constipation, diarrhea, or mixed constipation and diarrhea).[7] These bowel disorders can be distinguished from other GI disorders based on chronicity (having symptoms for 6 months or greater at the time of presentation), current activity (symptoms present within the last 3 months), frequency (symptoms present, on average, at least 1 day per week), and the absence of obvious anatomic or physiologic abnormalities identified by routine diagnostic examinations.[7] Constipation can arise secondary to neurological conditions, such as Parkinson disease and multiple sclerosis; endocrine disorders, such as hypothyroidism and hypercalcemia; and prescribed medications, such as opiates or tricyclic antidepressants.[8] The functional bowel disorders are classified into 5 distinct categories: IBS, chronic idiopathic constipation (CIC), functional diarrhea, functional abdominal bloating/distention, and unspecified bowel disorder.[7] A sixth category, OIC, is distinct from the other bowel disorders because it has a specific etiology that can produce symptoms similar to CIC.[7]

Functional, idiopathic, constipation is a chronic disorder in which symptoms of difficult, infrequent, or incomplete defecation predominate.[7] Patients with CIC do not meet IBS criteria, although abdominal pain or bloating may be present but are not predominant symptoms.[7] In adults, the mean prevalence rate of CIC is approximately 14%.[7] Risk factors for CIC include female sex, reduced caloric intake, and increasing age.[7] The Rome III criteria[9,10] are used to define functional constipation by the presence of the following 3 conditions for at least 3 months:

- Insufficient criteria for irritable bowel syndrome
- Without the use of laxatives, loose stools are rarely present
- Presence of 2 or more of the following criteria:
    - straining during ≥ 25% of defecations
    - lumpy or hard stools during ≥ 25% of defecations
    - feeling of incomplete evacuation during ≥ 25% of defecations
    - feeling of anorectal obstruction or blockage during ≥ 25% of defecations
    - manually facilitating defecation during ≥ 25% of defecations
    - less than 3 unassisted bowel movements/week

Treatment of CIC should begin by educating the patient about constipation, eliminating medications (prescription, over-the-counter, complementary) that can cause or worsen constipation and asking the patient to maintain a diet that contains an adequate amount of fiber.[7] Insoluble, non-fermentable fiber accelerates intestinal transit by increasing stool biomass leading to direct stimulation of secretion and motility.[7] Constipated patients with severely delayed colon transit or

obstructed defection are less likely to improve with fiber.[7] If a patient fails fiber therapy, laxative therapy can be initiated.[7] Laxatives either increase stool water content or accelerate bowel transit to alleviate constipation.[8] They are subdivided into 6 different categories depending on their mechanism of action:

- bulk-forming: calcium polycarbophil, methylcellulose, and psyllium
- lubricant: mineral oil
- stool softener: docusate
- stimulant: bisacodyl or senna
- osmotic: glycerin, lactulose, PEG, and sorbitol
- saline: magnesium hydroxide, magnesium citrate, and sodium phosphate

Irritable bowel syndrome is a disorder in which recurrent abdominal pain is associated with defecation or a change in bowel habits.[7] Disordered bowel habits are typically present (i.e., constipation, diarrhea, or a mix of constipation and diarrhea), as are symptoms of abdominal bloating or distention.[7] Symptom onset typically occurs at least 6 months before diagnosis and symptoms are present for at least 3 months. The world-wide prevalence of IBS is 11.2%.[7] Prevalence rates are higher for women than for men and younger people are more likely to be affected than those older than age 50 years.[7] Factors that trigger the onset or exacerbation of IBS symptoms include a prior gastroenteritis, food intolerances, chronic stress, diverticulitis, and surgery.[7] Therapeutic options to treat IBS-C include the prosecretory medications linaclotide and plecanatide. Linaclotide and plecanatide activate the cystic fibrosis transmembrane conductance regulator chloride channel by increasing luminal cyclic guanosine monophosphate.[8] Consequently, intestinal fluid is increased and intestinal transit is accelerated. An additional drug with Food and Drug Administration (FDA) approval for IBS-C is lubiprostone, a locally acting chloride channel activator that enhances intestinal fluid secretion and intestinal motility.

Tegaserod and prucalopride are 5-hydroxytryptamine-4 (5-HT4) receptor agonists which stimulate GI and colonic motility.[8] Tegaserod is FDA-approved for treatment of IBS-C and prucalopride is FDA approved for treatment of CIC. Tegaserod was withdrawn from the United States market in 2007 due to concerns involving possible cardiovascular adverse events. In 2019, tegaserod was re-introduced to the US market after FDA re-approval for use in IBS-C in women under 65 years of age. Prucalopride has been approved by the European Medicines Agency for the treatment of CIC in women since 2009. Prucalopride received FDA-approval in 2018 for treatment of CIC in adults. National Institute for Health and Care Excellence (NICE) guidance from 2010 recommends prucalopride as an option for the treatment of chronic constipation only in women for whom invasive treatment for constipation is being considered and after treatment failure with at least 2 laxatives from different classes, at the highest tolerated recommended doses for at least 6 months.[11]

Opioid-induced constipation has been defined by Rome IV criteria as a change from baseline bowel habits and defecation patterns after initiating opioid therapy, characterized by any of the following: reduced bowel frequency [less than 3 spontaneous bowel movements (SBMs) per week]; development or worsening of straining to pass a bowel movement; a sense of incomplete evacuation; or a patient's perception of distress related to bowel habits.[7] The occasional patient may also develop fecal impaction with overflow incontinence, while others may report symptoms compatible with overlapping opioid-induced bowel disorders (e.g., reflux, nausea, bloating).[7] In a systematic review of 8 placebo-controlled trials, the prevalence of OIC was 41% in patients with chronic non-cancer pain taking opioids.[12] In a study of cancer patients taking opioids for pain, the incidence of constipation was approximately 94%.[13] Three different classes of opioid receptors mediate the GI effects of opioid medications: kappa, delta and mu.[6] Opioids exert their GI effects via kappa-receptors in the stomach and small intestine and mu-receptors located in the small intestine and proximal colon.[6]

The initial treatment of OIC is similar to the treatment of CIC. Stimulant laxatives as monotherapy or in combination with a stool softener are initially recommended for both the prophylaxis and management of OIC in patients with cancer. Bulk-forming laxatives for not recommended for OIC due to the

increased risk of bowel obstruction. Peripheral-acting mu-opioid-receptor antagonists (i.e., methylnaltrexone, naloxegol, and naldemedine) are FDA-approved for the treatment of OIC in adults with non-cancer pain. These drugs block opioid receptors in the GI tract, antagonizing the constipating effects of opioids in the periphery without affecting analgesia. Another MOA, alvimopan, is only indicated for short-term use to prevent or decrease the course of postoperative ileus after bowel resection and is therefore available for hospital use only.[12] Lubiprostone is also FDA-approved for OIC in patients with chronic, non-cancer pain. A summary of GI drugs approved to treat CIC, IBS-C, and OIC for outpatient use is presented in **Table 1** (excluding laxatives)**.**

Table 1. Gastrointestinal Drugs FDA-Approved for Treatment of Constipation in an Outpatient Setting[14,15]

Generic (Brand Name)	Indications	Dosing	Boxed Warning
Guanylate Cyclase-C Agonists			
Linaclotide (LINZESS)	CIC IBS-C	72- 145 mcg po once daily 290 mcg po once daily	Serious Dehydration in Pediatric Patients: Use is contraindicated in pediatric patients <6 years. Avoid use in pediatric patients 6 to 17 years of age.
Plecanatide (TRULANCE)	CIC IBS-C	3 mg po once a day 3 mg po once a day	Serious Dehydration in Pediatric Patients: Use is contraindicated in pediatric patients <6 years. Avoid use in pediatric patients 6 to 17 years of age.
Chloride Channel Activator			
Lubiprostone (AMITIZA)	CIC IBS-C OIC: chronic, non-cancer pain	24 mcg po twice daily Females > 18 yo: 8 mcg po twice daily 24 mcg po twice daily	
Peripherally Acting Mu-Opioid Antagonists			
Naldemedine (SYMPROIC)	OIC: chronic, non-cancer pain	0.2 mg once daily	
Naloxegol (MOVANTIK)	OIC: chronic, non-cancer pain	25 mg once daily	
Methylnaltrexone (RELISTOR)	OIC with advanced illness (injection only) OIC with chronic non-cancer pain (tablets and injection)	450 mg po once daily 12 mg SC once daily	
Serotonin 5-HT(4) Receptor Agonists			
Prucalopride (MOTEGRITY)	CIC	2 mg po once daily	
Tegaserod (ZELNORM)	IBS-C	Females < 65 yo: 6 mg po twice daily	
Sodium/Hydrogen Exchanger			
Tenapanor (IBSRELA)	IBS-C	50 mg po twice daily	Serious Dehydration in Pediatric Patients: Use is contraindicated in pediatric patients <12 years. Avoid use in pediatric patients 6 to 17 years of age.

Abbreviations: 5HT (4) = 5-hydroxytryptamine; CIC = chronic idiopathic constipation; IBS-C = irritable bowel syndrome with constipation; mcg = micrograms; mg = milligrams; OIC = opioid induced constipation; po = oral; SC = subcutaneous; yo = years old

Objective measures that assess the severity of constipation and its impact on quality of life may help providers decide on course of treatment or whether to pursue more diagnostic studies.[16] Although the Rome criteria are used to identify constipation and its subtypes, they do not assess severity of the condition.[16] Many measures have been developed to assess constipation specifically, with variable psychometric properties. These include the Constipation Assessment Scale, Constipation Scoring System, Patient Assessment of Constipation Symptom Questionnaire, Knowles-Eccersley-Scott Symptom Score, Garrigues Questionnaire, Chinese Constipation Questionnaire, and Constipation Severity Instrument.[16] Other measures assess all bowel function and incorporate measures of fecal incontinence or specifically address one aspect of constipation, such as obstructive defecation. The purpose of all of these measures is simply to develop a consistent means of categorizing the baseline severity of the disease and to follow response to treatment over time.[16]

Methods:

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

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

New Systematic Reviews:

Cochrane: Osmotic and Stimulant Laxatives for the Management of Childhood Constipation

A 2018 Cochrane systematic review updated a 2012 publication which evaluated safety and efficacy of osmotic (PEG, milk of magnesia, lactulose) and stimulant (cascara, senna, bisacodyl, mineral oil) laxatives in children aged 0 to 18 years with chronic constipation.[1] The literature search was conducted through March 2016. The primary outcome was frequency of defecation (number of stools per week). Secondary endpoints included fecal incontinence, disimpaction, need for additional therapies and adverse events.[1] Twenty-five RCTs (n=2310 participants) met inclusion criteria.[1] Fourteen studies were judged to be at high risk of bias due to lack of blinding, small population size, incomplete outcome data and selective reporting.[1]

A meta-analysis of two studies (n=101 patients) comparing PEG with placebo showed a significantly increased number of stools per week with PEG [mean difference (MD) 2.61 stools per week, 95% CI 1.15 to 4.08, I^2=58%; low quality of evidence due to sparse data and inconsistency].[1] Common adverse events in the 2 studies included flatulence, abdominal pain, nausea, diarrhea and headache with no differences in incidence rates between the 2 groups.[1] Meta-analysis of 6 studies (n=465 participants) comparing PEG with lactulose showed more stools per week with PEG (MD 0.70, 95% CI 0.10 to 1.31, I^2=69%), although follow-up was short (4 weeks); [low quality of evidence due to inconsistency and high risk of bias (lack of blinding and selective reporting)].[1] No serious adverse events were reported with either agent. Common adverse events in these studies included diarrhea, abdominal pain, nausea, vomiting and anal itching.[1] There was no statistically significant difference in the proportion of patients who experienced at least one adverse event; 37% of PEG patients experienced at least one adverse event compared to 45% of lactulose patients [RR 0.87, 95% CI 0.68 to 1.11; low quality of evidence due to sparse data (100 events)].[1] A meta-analysis of 3 studies with 211 participants compared PEG with milk of magnesia which showed PEG resulted in more stools per week (MD 0.69, 95% CI 0.48 to 0.89, I^2=0%).[1] Overall, quality of the evidence was low due to sparse data and a high risk of bias (lack of blinding in one study and lack of blinding, incomplete outcome data and selective reporting in the other study).[1] No serious adverse events were reported.[1]

One study found a significant difference in number of stools per week favoring milk of magnesia over lactulose at 5 weeks [MD -1.51, 95% CI -2.63 to -0.39, 50 patients; low quality of evidence due to sparse data and a high risk of bias (lack of blinding and allocation concealment)].[1] A meta-analysis of 2 studies (n=287) comparing mineral oil with lactulose revealed a relatively large statistically significant difference in the number of stools per week favoring mineral oil [MD 4.94, 95% CI 4.28 to 5.61, I^2=0%; low quality of evidence due to sparse data and high risk of bias (lack of blinding in both studies)].[1] No serious adverse events were reported.[1] No statistically significant differences in the number of stools per week were found between dietary fiber mix and lactulose (1 study, 125 patients), senna and lactulose (1 study, 21 patients), PEG and dietary fiber (1 study, 83 patients; MD 0.20, 95% CI -0.64 to 1.04), and PEG and mineral oil (2 studies, 261 patients; MD 0.35, 95% CI -0.24 to 0.95).[1]

In summary, the pooled analyses from 11 RCTs suggest that PEG may be superior to placebo, lactulose and milk of magnesia for childhood constipation.[1] However, the overall quality of the evidence for the primary outcome (number of stools per week) was low or very low due to sparse, heterogeneous data, short follow-up and high risk of bias in the studies.[1] Low quality evidence also suggests mineral oil may be efficacious.[1] There is no evidence to assess efficacy of lactulose relative to other agents and there is a lack of placebo-controlled studies.[1] Further research is needed to investigate the relative efficacy of these agents for childhood constipation.[1]

Cochrane: Mu-Opioid Antagonists in Opioid Induced Constipation in Adults with Cancer or Receiving Palliative Care

A 2018 Cochrane update evaluated safety and efficacy of MOAs for alleviating OIC in adults with cancer or receiving palliative care.[2] The trials evaluated oral naldemedine and naloxone, and subcutaneous methylnaltrexone.[2] The literature search was completed through August 2017. Four new trials were identified for this update, bringing the total number included in the review to eight trials involving 1022 adults. All trials were vulnerable to biases; four were at a high risk of bias as they involved a sample of fewer than 50 participants per arm.[2] All 8 trials had unclear risk of selection bias as they under-reported allocation concealment or random sequence generation (or both), and 7 trials were at an unclear risk of reporting bias as they did not provide a protocol.[2] The primary efficacy outcome was bowel movement (BM) in the first 24 hours and between days 1 and 14 after the first dose.[2] Secondary outcomes included number of subjects who dropped out due to adverse effects, bowel transit time, relief of abdominal pain, and use of rescue medication for BM.

One trial (n=225) compared 3 doses of naldemedine (0.1 mg, 0.2 mg, or 0.4 mg) once daily to placebo in patients with cancer when conventional laxatives had failed. Overall, there were more spontaneous BM over the 2-week treatment period for the naldemedine group (RR 1.93, 95% CI 1.36 to 2.74, NNT=3; moderate-quality evidence).[2] Lower doses resulted in fewer spontaneous BMs than higher doses (0.1 mg vs. 0.2 mg: RR 0.73, 95% CI 0.55 to 0.95; 0.1 mg vs. 0.4 mg: RR 0.69, 95%CI 0.53 to 0.89; moderate-quality evidence).[2] The proportion of participants who had a rescue-free BM over the 2 weeks differed by dose of naldemedine, with the higher dose resulting in more BMs (0.1 mg: 56.4%; 0.2 mg: 77.6%; 0.4 mg: 82.1%; moderate-quality evidence).[2] There was moderate-quality evidence that naldemedine had no effect on opiate withdrawal over 2 weeks (0.1 mg: MD -0.13, 95% CI -0.57 to 0.31; 0.2 mg: MD -0.40, 95% -0.87 to 0.07; 0.4 mg: MD -0.02, 95% CI -0.45 to 0.41).[2] There were 5 serious adverse events with naldemedine but it was not clear if the any of the events were medication-related (low-quality evidence).[2] There was a higher incidence of non-serious adverse events (abdominal pain, nausea, and vomiting) in the naldemedine groups compared to placebo (RR 1.36, 95% CI 1.04 to 1.79, moderate-quality evidence).[2] The most common adverse event was diarrhea, but there was no difference in the proportion of patients impacted in either arm (RR 1.58, 95% CI 0.97 to 2.57, moderate-quality evidence).[2]

Two trials (n=287) compared methylnaltrexone to placebo in palliative care patients with OIC in which conventional laxatives had failed.[2] In the combined analysis, methylnaltrexone induced more BMs within 24 hours of the first dose compared to placebo (RR 2.77, 95% CI 1.91 to 4.04, I^2=0%; moderate-quality evidence).[2] In the combined analysis, methylnaltrexone induced more BMs over 2 weeks (RR 9.98, 95% CI 4.96 to 20.09, I^2=0%; moderate-quality evidence).[2] The

proportion of participants who had a rescue-free BM response within 24 hours of the first dose was 59.1% in the methylnaltrexone arm and 19.5% in the placebo arm.[2] There was moderate-quality evidence that the rate of opioid withdrawal was not affected.[2] There was no difference in the proportion of participants who experienced an adverse event between methylnaltrexone and placebo (RR 1.17, 95% CI 0.94 to 1.45; I^2=74%; low-quality evidence).[2] However, methylnaltrexone increased the likelihood of abdominal pain and flatulence compared to placebo (RR 2.39, 95% CI 1.07 to 5.34 and RR 2.09, 95% CI 1.07 to 4.08 respectively; low-quality evidence).[2]

In summary, there is moderate-quality evidence from one trial that suggested naldemedine improves bowel function in OIC for patients with cancer in whom conventional laxatives had failed, but at the increased risk of adverse events.[2] There is moderate-quality evidence from 2 trials that methylnaltrexone improves bowel function in people receiving palliative care with OIC and low-quality evidence that it does not increase adverse events.[2] There is insufficient evidence to assess the efficacy of naloxone as OIC trials with naloxone did not assess laxation.[2]

Efficacy of Treatments for Opioid-Induced Constipation

A high quality systematic review published in 2018 updated a previously published meta-analysis that evaluated the efficacy of medications approved to treat OIC.[3] The literature search included evidence published through March 2017. Twenty-six placebo-controlled RCTs evaluating methylnaltrexone, naloxone, naloxegol, alvimopan, prucalopride, lubiprostone, and naldemedine met inclusion criteria.[3] Over 9000 patients were enrolled in these trials. Baseline narcotic daily doses ranged from morphine equivalents of 20 to 2000 mg.[3] Opioid types varied from oxycodone to morphine to methadone.[3] Most of the RCTs provided moderate to high quality evidence.[3] Concerns about randomization, allocation concealment, and blinding in some of the studies resulted in a downgrade of quality assessment.[3] Two definitions of OIC were accepted including constipation associated with initiation of opioids, and fewer than 3 SBMs per week with at least one symptom of constipation (e.g., hard stools, sensation of incomplete evacuation, or moderate to severe straining in 25% of bowel movements after initiation of opioids).[3] The primary outcome was defined as treatment failure compared with placebo.[3] The most common primary outcome was 3 or more complete SBMs a week over the trial period.[3] Secondary efficacy outcomes included overall adverse events as well as individual rates of diarrhea, abdominal pain, nausea, and vomiting.[3]

A total of 1619 patients participated in the 6 methylnaltrexone trials. Patients received dosages of methylnaltrexone ranging from 12 mg to 450 mg, over 0.5 to 4 weeks in duration.[3] Of the 1004 individuals who received methylnaltrexone, 48% failed to respond (response defined as ≥ 3 BMs per week) compared with 72% of who received placebo.[3] Methylnaltrexone was more efficacious than placebo but there was significant heterogeneity between studies (RR, 0.62; 95% CI, 0.49 to 0.78; P<0.001; I^2=77.2; moderate quality evidence).[3] Five trials (n=482) examined the use of naloxone in doses ranging from 2 to 40 mg once daily versus placebo over 3 to 12 week in patients with OIC. OF note, naloxone is not currently FDA-approved for use in OIC. A total of 44% of patients failed to respond to naloxone compared to 70% of patients on placebo (RR, 0.63; P<0.001; 95% CI not reported; I^2=0.0%; moderate-quality evidence).[3]

Four trials examined the efficacy of alvimopan compared with placebo in OIC. Overall, 433 of 1060 (40.8%) patients receiving alvimopan failed to respond compared with 280 of 519 (53.9%) patients on placebo.[3] Three trials evaluated dosages of 0.5 and 1 mg daily, but the fourth trial used both a 1- and 2-mg total daily dosage.[3] Alvimopan was more efficacious than placebo (RR 0.68; P<0.001, 95% CI not reported), with some heterogeneity between trials (I^2=56.3%).[3] Four RCTs compared naldemedine to placebo in OIC. Overall, 45% of patients on naldemedine failed to respond compared with 65% patients who received placebo (RR, 0.65; P<0.001; 95% CI not reported; moderate quality evidence) but there was significant heterogeneity across trials (I^2=79.6%).[3]

Three trials (n=1522) compared naloxegol with placebo.[3] Moderate quality evidence showed that 58% of patients who received naloxegol failed to respond, compared with 71% of patients who received placebo (RR, 0.77; 95% CI, 0.61 to 0.97; P=0.026).[3] The 2 trials that compared the 12.5- and 25-mg doses (the 2

doses currently approved by the FDA) did not find a significant difference in efficacy between doses (RR 1.11; 95% CI, 0.94–1.30; P=0.208).[3] There was significant heterogeneity among the 3 trials (I^2=86.4%).[3]

Lubiprostone was compared to placebo in 3 RCTs (n=1284).[3] Moderate quality evidence showed 62% of patients who received lubiprostone failed to respond compared with 69% of patients who received placebo (RR, 0.90; 95% CI, 0.83 to 0.97; P=0.005; I^2=0%).[3] Only one placebo-controlled, double-blind trial compared prucalopride with placebo.[3] This trial showed modest results in favor of prucalopride compared to placebo in treating OIC (RR, 0.88; 95% CI, 0.68 to 0.98; P=0.032).[3]

Twenty-three placebo-controlled RCTs provided data regarding adverse events experienced within each group. In these trials, 58% of participants given a drug experienced at least one new-onset adverse event, compared with 53% of those given placebo.[3] This difference was significant (incidence rate ratio, 1.10; 95% CI, 1.05 to 1.16; P<0.001), with an overall NNH of 21 and no significant heterogeneity across trials (I^2=0.0%).[3] The 3 most common adverse effects were diarrhea (8.5%), abdominal pain (12.8%), and nausea/vomiting (11.5%).[3] Participants who received a study drug were significantly more likely to experience all 3 adverse events compared with placebo (P=0.009, 95% CI not reported).[3] The overall drop-out rate owing to adverse events (only 20 studies reported these data) were 7.4% and 4.7% for drug and placebo, respectively (P=0.002, 95% CI not reported), resulting in an NNH of 36 (95% CI, 22 to 96).[3]

In summary, 51% of subjects who received an OIC treatment (MOAs, lubiprostone, or prucalopride) responded to therapy, compared with 33% of individuals randomized to placebo, for an overall NNT of 5 (95% CI, 4 to 7).[3] The overall relative risk for failure to respond to therapy was significantly lower for those who received drug rather than placebo treatment (RR, 0.70; 95% CI, 0.64 to 0.75).[3] Individually, the NNTs for lubiprostone, naloxegol, methylnaltrexone, naloxone, and naldemedine were as follows: 15 (95% CI, 9 to 51), 7 (95% CI, 4 to 6), 4 (95% CI, 3 to 6), 4 (95% CI, 4 to 6), and 5 (95% CI, 4 to 8), respectively.[3] Compared to other agents, lubiprostone had the least efficacy in treating OIC based on failure to respond to therapy. After pooled analysis of all treatments for OIC, adverse effects were significantly higher in those who received active drug compared with placebo, with a NNH of 20.[3] A limitation of this systematic review was the significant heterogeneity across 26 studies, likely owing to the inclusion of multiple agents, varying baseline opioid use, and different subject populations (cancer versus non–cancer-related pain).[3]

After review, 7 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses or failure to meet AMSTAR criteria),[17-24] wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines - High Quality Guidelines:

2018 American College of Gastroenterology: Management of Irritable Bowel Syndrome

The American College of Gastroenterology (ACG) coordinated a high quality systematic review to assess the efficacy of pharmacologic therapies in treatment of IBS.[4] Parallel-group RCTs that compared pharmacologic agents with placebo in adults over 16 years of age were included in the review. The literature search was completed in July 2017. Outcome measures included global assessment of IBS cure or improvement, abdominal pain cure or improvement, and global IBS symptom or abdominal pain scores. An unrestricted educational grant was provided to the ACG Institute for Clinical Research and Education from Allergan and Ironwood Pharmaceuticals.[4] In addition, several authors served as consultants or speakers for various manufacturers. The systematic review was drafted before funding was obtained.[4] Strong recommendations with moderate- to high-quality evidence are summarized below.

1. Fiber is recommended for overall symptom improvement in IBS patients (Recommendation: strong; Quality of evidence: moderate).[4] Psyllium, but not wheat bran, is recommended for overall symptom improvement in IBS patients (Recommendation: strong; Quality of evidence: moderate).[4] Poorly fermentable, soluble fiber remains an evidence-based treatment for IBS.[4] Insoluble fiber may exacerbate pain and bloating in IBS, and has no evidence for efficacy.[4] The low cost and lack of significant adverse effects makes soluble fiber a reasonable first-line therapy for IBS patients and, in combination with the moderate quality of evidence, is the basis of a strong recommendation.[4]

2. Linaclotide is recommended for overall symptom improvement in IBS-C patients (Recommendation: strong; Quality of evidence: high).[4] Four placebo-controlled RCTs at low risk of bias were identified (n=2867 patients).[4] Meta-analysis of the results from the 4 RCTs favored linaclotide over placebo for improvement of IBS symptoms (RR=0.81; 95% CI 0.77 to 0.85; NNT=6; I^2=0%).[4] All 4 trials reported on abdominal pain improvement as an endpoint, and linaclotide was favored over placebo (RR=0.82; 95% CI 0.75 to 0.89; NNT=8).[4] Adverse events were reported in 3 trials, and were more frequent in the linaclotide arm compared to placebo (RR=1.10; 95% CI 1.01 to 1.19).[4] Diarrhea occurred more frequently in the linaclotide arm compared to placebo (RR=6.81; 95% CI 4.69 to 9.90; NNH=7).[4]

3. Plecanatide is recommended for overall symptom improvement in IBS-C patients (Recommendation: strong; Quality of evidence: moderate).[4] Three RCTs (n=2612) were identified, 2 phase 3 RCTs published in press in a single article, and 1 dose ranging trial published in abstract form only.[4] The phase 3 RCTs had a low risk of bias.[4] Pooled data from the 2 RCTs suggests a positive effect of plecanatide on improving IBS symptoms compared to placebo (RR=0.88; 95% CI 0.84 to 0.92; NNT=10; I^2=0%).[4] Total adverse events data were not available for the 3 studies individually, but were pooled for the 2 RCTs.[4] Twenty-four percent of patients assigned to 3 mg once daily of plecanatide reported any adverse event, compared with 20% of those randomized to 6 mg once daily of plecanatide, and 19% of those allocated to placebo.[4] Rates of diarrhea were higher with plecanatide versus placebo (RR=4.22; 95% CI 1.29 to 13.76; NNH=33).[4]

4. Lubiprostone is recommended for overall symptom improvement in IBS-C patients (Recommendation: strong; Quality of evidence: moderate).[4] Three trials at low risk of bias were identified.[4] In a meta-analysis, lubiprostone was more effective than placebo in improving IBS symptoms (RR=0.91; 95% CI 0.87 to 0.95; NNT=13, I^2=0%).[4] Adverse events were reported by 66% of patients receiving lubiprostone compared with 58% of patients on placebo (RR=1.13; 95% CI 0.87 to 1.48).[4] The only symptom to occur more frequently with lubiprostone was diarrhea (NNH=10).[4] Only 1 trial reported the incidence of nausea but there was no significant difference in rates between lubiprostone and placebo.[4] This recommendation differs from the Canadian guideline, as CAG made a conditional recommendation to recommend use of lubiprostone in IBS-C due to insufficient comparative evidence and the high cost of lubiprostone.[5]

Canadian Association of Gastroenterology Clinical Practice Guideline for the Management of Irritable Bowel Syndrome

The CAG clinical practice guideline for management of IBS was based on a literature search conducted through March 2017.[5] The systematic review used by the ACG in 2014 was updated with new evidence to guide development of the guideline.[25] The consensus group was a diverse group of practitioners and included a patient representative. Written disclosures of any potential conflicts of interest for the 24 months before the consensus meeting were provided by all participants and made available to all group members.[5] Funding for the consensus group meeting was provided by unrestricted grants to the CAG by Allergan Canada Inc. and Proctor & Gamble Canada.[5] The CAG administered all aspects of the meeting, and the funding sources had no involvement in the process of drafting and approval of these guidelines.[5] Several authors reported participating on advisory boards or speaker's bureaus for various pharmaceutical manufacturers. Recommendations with moderate to high quality evidence are summarized below. Plecanatide was not evaluated because it is not commercially available in Canada.

1. Psyllium supplementation is recommended to improve IBS-C symptoms (Recommendation: Strong; Quality of evidence: Moderate).[5] For this recommendation, a prior systematic review and meta-analysis was updated with one additional RCT for a total of 15 RCTs (n=946).[5] Risk of bias was unclear in the majority of studies.[5] Overall, fiber supplementation was favored over placebo or no treatment (RR of IBS not improving 0.87; 95% CI, 0.80 to 0.94; P=0.0003).[5] In the updated meta-analysis (7 studies, n=606), there was no increase in overall adverse events with fiber compared with placebo (36.6% vs. 25.1%; RR 1.06; 95% CI 0.92 to 1.22).[5] There were insufficient data from individual studies to assess adverse events according to fiber type.[5] Based on the evidence for efficacy and safety, the consensus group strongly recommended soluble fiber supplementation as a low-cost, safe treatment option that is acceptable to patients and has moderate-quality evidence that it improves IBS symptoms.[5]

2. Lubiprostone is recommended to improve IBS symptoms (Recommendation: Conditional; Quality of evidence: Moderate). Evidence for lubiprostone is available from 3 RCTs in IBS-C patients (n=1366).[5] All 3 of the trials used Rome criteria to define IBS-C, and all were at low risk of bias.[5] One trial was a dose-range, phase 2 study that assessed lubiprostone 8–24 mcg twice daily, and two trials were phase 3 studies evaluating 8 mcg twice daily.[5] In the pooled analysis, lubiprostone was more effective than placebo (RR of IBS not improving 0.91; 95% CI 0.87–0.95; P<0.0001; NNT 12.4; 95% CI 8-25).[5] In the phase 2 study, there was moderate-quality evidence that lubiprostone improved overall IBS symptoms, but the effect on abdominal pain was only statistically significant for the first 2 months, but not the third month, of treatment.[5] No comparative studies have evaluated whether lubiprostone is more effective than other much less expensive treatment options, so the consensus group made a conditional recommendation in favor of lubiprostone in IBS-C patients.[5]

3. Linaclotide is recommended to improve IBS-C symptoms (Recommendation: Strong; Quality of evidence: High). For this recommendation, a prior systematic review and meta-analysis was updated with one additional RCT (n=172), for a total of 4 RCTs (n=2867).[5] All trials used Rome criteria to define IBS-C, and all were at low risk of bias.[5] In the pooled analysis, linaclotide was more effective than placebo (RR of IBS not improving 0.81; 95% CI 0.77 to 0.85; P<0.00001; NNT 6; 95% CI, 5 to 8).[5] Linaclotide also improved abdominal pain compared with placebo (RR for no improvement 0.82; 95% CI 0.75 to 0.89; P<0.001; NNT 8).[5] Adverse event data were available from 3 RCTs. The pooled incidence of any adverse event was significantly greater among patients who received linaclotide versus those who received placebo (49.6% vs. 45.2%; RR 1.10; 95% CI 1.01 to 1.19; NNH 12).[5] Linaclotide was associated with higher rates of diarrhea (4 studies; RR 6.81; 95% CI 4.69 to 9.90; NNH 7) and flatulence (2 studies; RR 2.27; 95% CI 1.18–4.36; NNH 50) compared with placebo.[5]

2019 American Gastroenterological Association: Medical Management of Opioid-Induced Constipation

The official recommendations of the American Gastroenterological Association (AGA) on the medical management of OIC were published in 2019. The guideline was developed by the AGA Institute's Clinical Guidelines Committee and approved by the AGA Governing Board. It is accompanied by a technical review that is a compilation of clinical evidence from which these recommendations were formulated.[6] Development of this guideline and its accompanying technical review was fully funded by the AGA Institute with no additional outside funding.[6] Recommendations are summarized in **Table 2.**

Table 2. Summary of Recommendations of the AGA Clinical Guidelines for the Medical Management of Opioid-Induced Constipation[6]

Recommendation	Strength of Recommendation	Quality of Evidence
Traditional Laxatives		
Laxatives recommended as first-line agents	Strong	Moderate
Opioid Receptor Antagonists		
Naldemedine recommended for laxative refractory OIC	Strong	High
Naloxegol recommended for laxative refractory OIC	Strong	Moderate

Methylnaltrexone recommended for refractory OIC	Conditional	Low
Chloride Channel Activator		
Insufficient evidence to recommend lubiprostone	No Recommendation	Evidence Gap
Selective 5-HT (4) Agonist		
Insufficient evidence to recommend prucalopride	No Recommendation	Evidence Gap

New Formulations or Indications:

1. Prucalopride (Motegrity™) tablets received FDA approval in December 2018. Prucalopride is a 5-HT4 agonist indicated for the treatment of CIC in adults.[26] The recommended dose is 2 mg orally, once daily in adults with normal renal function.[26] For patients with severe renal impairment (creatinine clearance less than 30 mL/min) the dose should be reduced to 1 mg once daily.[26] The most common adverse reactions (≥2%) are headache, abdominal pain, nausea, diarrhea, abdominal distension, dizziness, vomiting, flatulence, and fatigue.[26] Patients should be monitored for persistent worsening of depression and emergence of suicidal thoughts and behavior while taking prucalopride.[26] The drug should be discontinued if their depression is persistently worse or they experience emerging suicidal thoughts.

2. Tegaserod (Zelnorm™) was previously indicated for all women with IBS-C. Tegaserod was withdrawn from the United States market in 2007 due to concerns involving possible cardiovascular adverse events. In 2019, tegaserod was re-introduced to the US market after FDA re-approval for use in IBS-C in women under 65 years of age. [27] The safety and efficacy of tegaserod has not been established in men with IBS-C.[27] The recommended dose is 6 mg orally taken twice daily on an empty stomach. If patients have not an adequate response to tegaserod after 4 to 6 weeks of treatment, the drug should be discontinued.[27]

3. Tenapanor (Ibsrela®) tablets received FDA approval September 2019. Tenapanor is a sodium/hydrogen exchanger-3 (NHE3) inhibitor approved for the treatment of IBS-C in adults.[28] The recommended dose is 50 mg orally twice daily on an empty stomach.[28] The drug is contraindicated in pediatric patients less than 6 years of age or patients with a known or suspected mechanical GI obstruction.[28] The most serious adverse effects reported greater than or equal to 2% include severe diarrhea, abdominal distension, flatulence, and dizziness.[28]

4. Lactitol (Pizensy®) oral solution received FDA approval February 2020. Lactitol is an osmotic laxative indicated for the treatment of CIC in adults.[29] The approval is based on an 594-patient, six-month, randomized, placebo-controlled trial.[29] Most of the subjects enrolled in this trial were women (76%).[29]

The efficacy of lactitol was assessed using a responder analysis and change-from-baseline in the complete spontaneous bowel movements endpoint, using information provided by patients after each bowel movement in an electronic diary.[29] The primary efficacy analysis was based on the first 12 weeks of the 6-month treatment period for 594 patients.[29]A responder was defined as a patient who had at least 3 BMs in a given week and an increase of at least 1 BM from baseline in the same week for at least 9 weeks out of the first 12 weeks of treatment and at least 1 BM in at least 3 of the last 4 weeks of the treatment period.[29] Twenty-five percent of patients randomized to lactitol (n=291) responded to therapy compared with 13% of patients (n=303) in the placebo group (treatment difference: 12%, 95% CI 6.0 to 18.5, $p < 0.05$).[29]

In clinical testing, the most common adverse reactions were upper respiratory tract infections, flatulence, diarrhea, increased blood creatinine phosphokinase, abdominal distension, and increased blood pressure.[29]

New FDA Safety Alerts:

Table 3. Description of new FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Tegaserod[27]	Zelnorm®	3/19	Contraindications, Warnings and Precautions	**Contraindications:** Package label revised to include additional contraindications in patients with myocardial infarction (MI), stroke, transient ischemic attack (TIA), or angina. In addition, a history of colitis or other forms of intestinal ischemia were added as contraindications. **Warnings and Precautions:** 2 additional warnings and precautions were added to the tegaserod label. 1. Cardiovascular Ischemic Events: Stroke, MI, and cardiovascular death (major adverse cardiovascular events [MACE]) have been reported in adults taking tegaserod who had an increased risk of developing an adverse cardiovascular event based on their medical history. Tegaserod is contraindicated in patients with a history of MI, stroke, TIA, or angina. Assess female patients less than 65 years of age for a history of cardiovascular disease and cardiovascular risk factors prior to treatment with tegaserod.[27] 2. Suicidal Ideation and Behavior: Suicide, suicidal attempt and ideation, and self-injurious behavior have been reported in clinical trials of IBS-C and other gastrointestinal motility disorders. The frequency of suicidal ideation or attempts with tegaserod treatment (8 patients out of 10,003) was higher than placebo (1 patient out of 5,425). Suicidal ideation/behavior in clinical trials was proportionately more frequent among patients receiving antidepressant medication.[27] Monitor all tegaserod-treated patients for clinical worsening of depression and emergence of suicidal thoughts and behaviors, especially during the initial few months of treatment. Counsel family members and caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Instruct patients to immediately discontinue tegaserod and contact their healthcare provider if their depression is persistently worse or they are experiencing emergent suicidal thoughts or behaviors.[27]

Randomized Controlled Trials:

A total of 71 citations were manually reviewed from the initial literature search. After further review, 71 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

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29. Pizensy®(lactitol) Oral Solution Prescribing Information. Braintree, MA; Braintree Laboratories, Inc. February 2020.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
bisacodyl	LAXATIVE	TABLET	ORAL	Y
bisacodyl	LAXATIVE FEMININE	TABLET	ORAL	Y
bisacodyl	WOMEN'S LAXATIVE	TABLET	ORAL	Y
bisacodyl	BISACODYL	TABLET DR	ORAL	Y
bisacodyl	BISA-LAX	TABLET DR	ORAL	Y
bisacodyl	DUCODYL	TABLET DR	ORAL	Y
bisacodyl	GENTLE LAXATIVE	TABLET DR	ORAL	Y
bisacodyl	LAXATIVE	TABLET DR	ORAL	Y
bisacodyl	MODANE	TABLET DR	ORAL	Y
bisacodyl	WOMEN'S GENTLE LAXATIVE	TABLET DR	ORAL	Y
bisacodyl	WOMEN'S LAXATIVE	TABLET DR	ORAL	Y
calcium polycarbophil	FIBER	TABLET	ORAL	Y
calcium polycarbophil	FIBER LAXATIVE	TABLET	ORAL	Y
calcium polycarbophil	FIBER TABS	TABLET	ORAL	Y
calcium polycarbophil	FIBER-LAX	TABLET	ORAL	Y
calcium polycarbophil	KONSYL FIBER	TABLET	ORAL	Y
cellulose	UNIFIBER	POWDER	ORAL	Y
docusate calcium	DOCUSATE CALCIUM	CAPSULE	ORAL	Y
docusate calcium	KAOPECTATE	CAPSULE	ORAL	Y
docusate calcium	KAO-TIN	CAPSULE	ORAL	Y
docusate calcium	STOOL SOFTENER	CAPSULE	ORAL	Y
docusate sodium	COLACE	CAPSULE	ORAL	Y
docusate sodium	COLACE CLEAR	CAPSULE	ORAL	Y
docusate sodium	DOC-Q-LACE	CAPSULE	ORAL	Y
docusate sodium	DOCUSATE SODIUM	CAPSULE	ORAL	Y
docusate sodium	DOCUSIL	CAPSULE	ORAL	Y
docusate sodium	DOK	CAPSULE	ORAL	Y
docusate sodium	SOF-LAX	CAPSULE	ORAL	Y
docusate sodium	STOOL SOFTENER	CAPSULE	ORAL	Y
docusate sodium	DOCU LIQUID	LIQUID	ORAL	Y
docusate sodium	DOCUSATE SODIUM	LIQUID	ORAL	Y
docusate sodium	SILACE	LIQUID	ORAL	Y
docusate sodium	STOOL SOFTENER	LIQUID	ORAL	Y
docusate sodium	COLACE	SYRUP	ORAL	Y
docusate sodium	DOCUSATE SODIUM	SYRUP	ORAL	Y
docusate sodium	PEDIA-LAX STOOL SOFTENER	SYRUP	ORAL	Y
docusate sodium	SILACE	SYRUP	ORAL	Y

docusate sodium	STOOL SOFTENER	SYRUP	ORAL	Y
docusate sodium	DOCUSATE SODIUM	TABLET	ORAL	Y
docusate sodium	DOK	TABLET	ORAL	Y
docusate sodium	STOOL SOFTENER	TABLET	ORAL	Y
fructooligosaccharides/polydex	FIBEREX F15	LIQUID	ORAL	Y
lactulose	CONSTULOSE	SOLUTION	ORAL	Y
lactulose	ENULOSE	SOLUTION	ORAL	Y
lactulose	GENERLAC	SOLUTION	ORAL	Y
lactulose	LACTULOSE	SOLUTION	ORAL	Y
magnesium citrate	CITRATE OF MAGNESIA	SOLUTION	ORAL	Y
magnesium citrate	MAGNESIUM CITRATE	SOLUTION	ORAL	Y
magnesium hydroxide	MILK OF MAGNESIA	ORAL SUSP	ORAL	Y
magnesium hydroxide	PEDIA-LAX	TAB CHEW	ORAL	Y
methylcellulose	CITRUCEL	TABLET	ORAL	Y
methylcellulose	FIBER	TABLET	ORAL	Y
methylcellulose	FIBER LAXATIVE	TABLET	ORAL	Y
methylcellulose	FIBER THERAPY	TABLET	ORAL	Y
methylcellulose (with sugar)	FIBER THERAPY	POWDER	ORAL	Y
polyethylene glycol 3350	CLEARLAX	POWDER	ORAL	Y
polyethylene glycol 3350	GAVILAX	POWDER	ORAL	Y
polyethylene glycol 3350	GLYCOLAX	POWDER	ORAL	Y
polyethylene glycol 3350	NATURA-LAX	POWDER	ORAL	Y
polyethylene glycol 3350	POLYETHYLENE GLYCOL 3350	POWDER	ORAL	Y
psyllium husk	FIBER	CAPSULE	ORAL	Y
psyllium husk	FIBER LAXATIVE	CAPSULE	ORAL	Y
psyllium husk	KONSYL	CAPSULE	ORAL	Y
psyllium husk	NATURAL FIBER	CAPSULE	ORAL	Y
psyllium husk	KONSYL	POWDER	ORAL	Y
psyllium husk	KONSYL EASY MIX	POWDER	ORAL	Y
psyllium husk (with dextrose)	KONSYL FORMULA-D	POWDER	ORAL	Y
psyllium husk (with sugar)	FIBER	POWDER	ORAL	Y
psyllium husk (with sugar)	KONSYL	POWDER	ORAL	Y
psyllium husk (with sugar)	NATURAL FIBER	POWDER	ORAL	Y
psyllium husk (with sugar)	NATURAL FIBER LAXATIVE	POWDER	ORAL	Y
psyllium husk (with sugar)	NATURAL VEGETABLE POWDER	POWDER	ORAL	Y
psyllium husk (with sugar)	REGULOID	POWDER	ORAL	Y
psyllium husk/aspartame	FIBER	POWDER	ORAL	Y
psyllium husk/aspartame	NATURAL FIBER	POWDER	ORAL	Y
psyllium seed	FIBER SMOOTH	POWDER	ORAL	Y
psyllium seed	KONSYL	POWDER	ORAL	Y

psyllium seed	NATURAL VEGETABLE LAXATIVE	POWDER	ORAL	Y
psyllium seed	NATURAL VEGETABLE POWDER	POWDER	ORAL	Y
psyllium seed	NVP	POWDER	ORAL	Y
psyllium seed	REGULOID	POWDER	ORAL	Y
psyllium seed (with dextrose)	KONSYL-D	PACKET	ORAL	Y
psyllium seed (with dextrose)	FIBER	POWDER	ORAL	Y
psyllium seed (with dextrose)	KONSYL-D	POWDER	ORAL	Y
psyllium seed (with dextrose)	MODANE BULK	POWDER	ORAL	Y
psyllium seed (with dextrose)	NATURAL FIBER	POWDER	ORAL	Y
psyllium seed (with dextrose)	NATURAL VEGETABLE POWDER	POWDER	ORAL	Y
psyllium seed (with sugar)	FIBER SMOOTH	POWDER	ORAL	Y
psyllium seed (with sugar)	NATURAL FIBER	POWDER	ORAL	Y
psyllium seed (with sugar)	NATURAL FIBER POWDER	POWDER	ORAL	Y
psyllium seed (with sugar)	NATURAL PSYLLIUM LAXATIVE	POWDER	ORAL	Y
psyllium seed (with sugar)	NATURAL VEGETABLE LAXATIVE	POWDER	ORAL	Y
psyllium seed (with sugar)	NVP	POWDER	ORAL	Y
psyllium seed/aspartame	KONSYL	POWDER	ORAL	Y
psyllium seed/aspartame	NATURAL FIBER	POWDER	ORAL	Y
psyllium seed/sod bicarb	KONSYL EFFERVESCENT	PACKET	ORAL	Y
senna leaf extract	SENNA	SYRUP	ORAL	Y
senna/psyllium seed	PERDIEM	GRANULES	ORAL	Y
sennosides	SENNA	CAPSULE	ORAL	Y
sennosides	SENNA	SYRUP	ORAL	Y
sennosides	CHOCOLATED LAXATIVE	TAB CHEW	ORAL	Y
sennosides	EX-LAX	TAB CHEW	ORAL	Y
sennosides	EX-LAX	TABLET	ORAL	Y
sennosides	EX-LAX MAXIMUM STRENGTH	TABLET	ORAL	Y
sennosides	LAXATIVE	TABLET	ORAL	Y
sennosides	LAXATIVE MAXIMUM STRENGTH	TABLET	ORAL	Y
sennosides	NATURAL VEGETABLE LAXATIVE	TABLET	ORAL	Y
sennosides	PERDIEM	TABLET	ORAL	Y
sennosides	SENEXON	TABLET	ORAL	Y
sennosides	SENNA	TABLET	ORAL	Y
sennosides	SENNA LAX	TABLET	ORAL	Y
sennosides	SENNA LAXATIVE	TABLET	ORAL	Y
sennosides	SENNATURAL	TABLET	ORAL	Y
sennosides	SENNO	TABLET	ORAL	Y
sennosides	SENOKOT	TABLET	ORAL	Y
sennosides/docusate sodium	COLACE 2-IN-1	TABLET	ORAL	Y
sennosides/docusate sodium	DOCUSATE SODIUM-SENNA	TABLET	ORAL	Y

sennosides/docusate sodium	DOK PLUS	TABLET	ORAL	Y
sennosides/docusate sodium	SENEXON-S	TABLET	ORAL	Y
sennosides/docusate sodium	SENNA PLUS	TABLET	ORAL	Y
sennosides/docusate sodium	SENNA-S	TABLET	ORAL	Y
sennosides/docusate sodium	SENNA-TIME S	TABLET	ORAL	Y
sennosides/docusate sodium	SENNOSIDES-DOCUSATE SODIUM	TABLET	ORAL	Y
sennosides/docusate sodium	SENOKOT-S	TABLET	ORAL	Y
sennosides/docusate sodium	STOOL SOFTENER-LAXATIVE	TABLET	ORAL	Y
sennosides/docusate sodium	STOOL SOFTENER-STIMULANT LAX	TABLET	ORAL	Y
sennosides/docusate sodium	VEGETABLE LAX-STOOL SOFTENER	TABLET	ORAL	Y
sennosides/psyllium husk	SENNA PROMPT	CAPSULE	ORAL	Y
wheat dextrin	BENEFIBER	POWD PACK	ORAL	Y
wheat dextrin	BEST FIBER	POWDER	ORAL	Y
alvimopan	ENTEREG	CAPSULE	ORAL	N
bran	BRAN	TABLET	ORAL	N
bran	OAT BRAN FIBER	TABLET	ORAL	N
casanthranol/docusate sodium	DOCUSATE SODIUM W/CASANTHRANOL	CAPSULE	ORAL	N
casanthranol/docusate sodium	DOCUSATE SODIUM-CASANTHRANOL	CAPSULE	ORAL	N
casanthranol/docusate sodium	PERI-COLACE	CAPSULE	ORAL	N
casanthranol/docusate sodium	STOOL SOFTENER W/LAXATIVE	CAPSULE	ORAL	N
cascara sagrada/mag hydrox	MILK OF MAGNESIA W/CASCARA	ORAL SUSP	ORAL	N
castor oil	CASTOR OIL	OIL	ORAL	N
dextrin	FIBER	POWDER	ORAL	N
lactulose	KRISTALOSE	PACKET	ORAL	N
linaclotide	LINZESS	CAPSULE	ORAL	N
lubiprostone	AMITIZA	CAPSULE	ORAL	N
methylcellulose	CITRUCEL	POWDER	ORAL	N
methylcellulose	FIBER THERAPY	POWDER	ORAL	N
methylcellulose (with sugar)	CITRUCEL	POWDER	ORAL	N
methylcellulose (with sugar)	FIBER THERAPY	POWDER	ORAL	N
methylnaltrexone bromide	RELISTOR	SYRINGE	SUB-Q	N
methylnaltrexone bromide	RELISTOR	TABLET	ORAL	N
methylnaltrexone bromide	RELISTOR	VIAL	SUB-Q	N
mineral oil	MINERAL OIL	OIL	ORAL	N
naldemedine tosylate	SYMPROIC	TABLET	ORAL	N
naloxegol oxalate	MOVANTIK	TABLET	ORAL	N
plecanatide	TRULANCE	TABLET	ORAL	N
polyethylene glycol 3350	CLEARLAX	POWD PACK	ORAL	N
polyethylene glycol 3350	HEALTHYLAX	POWD PACK	ORAL	N
polyethylene glycol 3350	POLYETHYLENE GLYCOL 3350	POWD PACK	ORAL	N

polyethylene glycol 3350	SMOOTHLAX	POWD PACK	ORAL	N
psyllium husk	REGULOID	CAPSULE	ORAL	N
psyllium husk	KONSYL	POWD PACK	ORAL	N
psyllium husk (with sugar)	KONSYL	POWD PACK	ORAL	N
prucalopride succinate	MOTEGRITY	TABLET	ORAL	
tegaserod hydrogen maleate	ZELNORM	TABLET	ORAL	

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to December Week 1 2019, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 17, 2019

1.	*Bisacodyl/*	*163*
2.	*Calcium polycarbophil.mp.*	*96*
3.	*Cellulose/*	*15464*
4.	*Docusate.mp. or Dioctyl Sulfosuccinic Acid/*	*406*
5.	*Lactulose/*	*1012*
6.	*Magnesium citrate.mp.*	*277*
7.	*Magnesium Hydroxide/ or Aluminum Hydroxide/ or Calcium Carbonate/*	*6286*
8.	*Methylcellulose/*	*1965*
9.	*Polyetheylene glycol.mp.*	*2*
10.	*Psyllium.mp. or Psyllium/*	*497*
11.	*Senna.mp. or Senna Extract/*	*536*
12.	*Wheat dextrin.mp.*	*19*
13.	*Alvimopan.mp.*	*196*
14.	*Castor Oil/*	*511*
15.	*Dextrins/*	*362*
16.	*Lactulose/*	*1012*
17.	*linaclotide.mp.*	*261*
18.	*Lubiprostone/*	*153*
19.	*Methylcellulose/*	*1965*
20.	*methylnaltrexone.mp.*	*301*
21.	*Mineral Oil/*	*643*
22.	*naldemedine.mp.*	*39*
23.	*naloxegol.mp.*	*99*
24.	*plecanatide.mp.*	*56*
25.	*Casanthranol.mp. or Cascara/*	*15*
26.	*prucalopride.mp.*	*321*
27.	*Sodium phosphate.mp.*	*3459*
28.	*tegaserod.mp.*	*408*
29.	*Gastrointestinal Motility/ or Irritable Bowel Syndrome/*	*12214*
30.	*Constipation/*	*7872*
31.	*1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28*	*32566*
32.	*29 or 30*	*18976*
33.	*31 and 32*	*1199*
34.	*limit 35 to (english language and humans and yr="2016 -Current" and (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or comparative study or meta-analysis or multicenter study or randomized controlled trial or "systematic review"))*	*71*

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-10: K3183-3184, K310, R1110, K30, K3189, K319, K314-315, K312, K589, K591, K594, K5900-5902, K5909, K910-911, K9189, K598-599, R159, R150, R152)

Requires PA:

- Non-preferred drugs

Covered Alternatives:

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

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

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.

Approval Criteria

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.
   - Naldemedine (SYMPROIC): Opioid-induced constipation in patients with non-cancer pain is not approvable. Justification must be 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.
   - Plecanatide (TRULANCE): Chronic idiopathic 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.
   - Prucalopride (MOTEGRITY): Chronic idiopathic 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.
   - Tegaserod (ZELNORM): Constipation secondary to irritable bowel syndrome is not approvable. Justification must be provided for not meeting criterion #4.
   - Tenapanor (ISBRELA): Constipation secondary to irritable bowel syndrome is not approvable. Justification must be provided for not meeting criterion #4.

P&T Review: *6/20 (DM), 7/17 (DM); 3/15; 3/09*
Implementation: *7/1/20; 9/1/17; 5/1/16; 10/15, 4/18/15*