Inland Empire Health Plan

Drug Class Monograph

Class: Irritable Bowel Syndrome Agents
Drug: Amitiza (lubiprostone), Hyoscymine, Linzess (linaclotide), Viberzi (eluxadoline), Xifaxan (rifaximin)
Formulary Medication: Bisacodyl, Fiber, Lactulose, Polyethylene glycol, Psyllium, Senna
Line of Business: Non-Medicare
Effective Date: November 16, 2016
Renewal Date: November 16, 2016

This policy has been developed through review of medical literature, consideration of medical necessity, generally accepted medical practice standards, and approved by the IEHP Pharmacy and Therapeutics Subcommittee.

Policy/Criteria:

1. Amitiza (lubiprostone)
   a. Confirmed diagnosis of irritable bowel syndrome-related constipation (female only) or idiopathic chronic constipation;
      i. Failure or clinically significant adverse effects to two of the following:
         • Fiber (e.g. psyllium, methylcellulose, etc.);
         • Osmotic laxative (e.g. polyethylene glycol, lactulose);
         • Stimulant laxative (e.g. bisacodyl, senna);
      ii. Failure or clinically significant adverse effects to Linzess.

   b. Confirmed diagnosis of opioid-induced constipation in adults with chronic, non-cancer pain;
      i. Failure or clinically significant adverse effects to two of the following:
         • Fiber (e.g. psyllium, methylcellulose, etc.);
         • Osmotic laxative (e.g. polyethylene glycol, lactulose);
         • Stimulant laxative (e.g. bisacodyl, senna).

2. Linzess (linaclotide)
   a. Confirmed diagnosis of irritable bowel syndrome-related constipation or idiopathic chronic constipation;
      i. Failure or clinically significant adverse effects to two of the following:
         • Fiber (e.g. psyllium, methylcellulose, etc.);
         • Osmotic laxative (e.g. polyethylene glycol, lactulose);
         • Stimulant laxative (e.g. bisacodyl, senna).
3. **Viberzi (eluxadoline)**
   a. Confirmed diagnosis of irritable bowel syndrome with diarrhea:
      i. Failure or clinically significant adverse effects to loperamide;
      ii. Prescribed by a gastroenterologist.

4. **Xifaxan (rifaximin)**
   a. Confirmed diagnosis of irritable bowel syndrome with diarrhea:
      i. Failure or clinically significant adverse effects to loperamide;
      ii. Prescribed by a gastroenterologist.
   
   b. Confirmed diagnosis of hepatic encephalopathy:
      i. Failure or clinically significant adverse effects to lactulose;
      ii. Prescribed by a gastroenterologist or hepatologist.
   
   c. Confirmed diagnosis of traveler’s diarrhea:
      i. Failure or clinically significant adverse effects to ciprofloxacin for patients of age 18 or older.

**Clinical Justification:**

**Comparison of FDA Approved Indications**

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<th>Drug</th>
<th>FDA Approved Indications</th>
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| Amitiza (lubiprostone) | Chronic idiopathic constipation in adults  
Opioid induced constipation in adults with chronic non-cancer pain  
Irritable bowel syndrome with constipation in women 18 years of age or older                                        |
| Linzess (linaclotide) | Irritable bowel syndrome with constipation in adults  
Chronic idiopathic constipation in adults                                                                                                                           |
| Lotronex (alosetron)  | Severe diarrhea-predominant irritable bowel syndrome in women who have:  
  - Chronic IBS (generally lasting 6 months or longer)  
  - Had anatomic or biochemical abnormalities of the GI tract excluded, and  
  - Not responded adequately to conventional therapy |
| Viberzi (eluxadoline) | Irritable bowel syndrome with diarrhea (IBS-D)                                                                                                                     |
| Xifaxan (rifaximin)   | Traveler’s diarrhea caused by noninvasive strains of E coli in adults and pediatric patients 12 years of age or older  
Reduction in hepatic encephalopathy recurrence in adults  
Irritable bowel syndrome with diarrhea (IBS-D) in adults                                              |
**American College of Gastroenterology Monograph on the Management of Irritable Bowel Syndrome and Chronic Idiopathic Constipation 2014**

**Irritable Bowel Syndrome:**
- Fiber provides overall symptom relief in IBS.
- Psyllium, but not bran, provides overall symptom relief in IBS.
  - Insoluble fibers may exacerbate symptoms and provide little relief; soluble fiber and psyllium, in particular, provide relief in IBS.
- There is insufficient evidence to recommend prebiotics or synbiotics in IBS.
- Probiotics in IBS taken as a whole improve global symptoms, bloating and flatulence in IBS.
- The poorly absorbable antibiotic rifaximin is effective at reducing total IBS symptoms and bloating in diarrhea predominant IBS.
- Certain antispasmodics (hyoscine, dicyclomine) provide symptomatic short-term relief in IBS. Adverse events are more common with antispasmodics than placebo.
- Although loperamide is an effective antidiarrheal, there is insufficient evidence to recommend loperamide for relief of global symptoms in IBS.
- Alosetron is effective in females with diarrhea-predominant IBS.
  - Because of concerns regarding adverse events, the use of alosetron in the United States is limited to women with severe diarrhea-predominant IBS and can be prescribed only in the context of a carefully monitored program.
- Linaclotide is superior to placebo for the treatment of constipation-predominant IBS.
- Lubiprostone is superior to placebo for the treatment of constipation-predominant IBS.
- There is no evidence that PEG improves overall symptoms and pain in patients with IBS.
  - PEG is a large polymer that behaves as an osmotic laxative, and although it is approved by the FDA for the treatment of occasional constipation, it has not been extensively studied in patients with IBS-C.

**Chronic Idiopathic Constipation:**
- Fiber and soluble fiber, in particular, are effective in the management of chronic constipation. Adverse events and bloating, distension, flatulence, and cramping may limit the use of insoluble fiber, especially if increases in fiber intake are not introduced gradually.
- Although supported by varying levels of evidence, the osmotic laxatives PEG and lactulose and the stimulant laxatives sodium picosulfate and bisacodyl have been shown to be effective in chronic constipation.
- The prosecretory agents, linaclotide and lubiprostone, are effective in CIC and are well tolerated. There have been no comparative studies.
- There is insufficient evidence to recommend probiotics in CIC.
**Viberzi (eluxadoline)**

- Eluxadoline, a mixed mu-opioid receptor agonist with delta-opioid receptor antagonist and kappa opioid receptor agonist effects, was FDA approved for treatment of irritable bowel syndrome with diarrhea (IBS-D). It is classified as a schedule IV substance by the DEA.
- Efficacy was demonstrated in two multicenter, double-blinded, placebo-controlled randomized clinical trials. A total of 1281 patients in study 1 and 1145 patients in Study 2 received eluxadoline 75mg, 100mg or placebo twice daily. The primary endpoint was defined by the simultaneous improvement in the daily worst abdominal pain score by ≥30% as compared to the baseline weekly average and a reduction in the BBS to <5 on at least 50% of the days within a 12-week time interval. In 26 weeks, a significantly more patients receiving eluxadoline 100mg twice daily achieved the primary end point in comparison to the placebo group in both studies (29% vs. 19%; 33% vs. 20%). Common adverse events associated with eluxadoline were nausea, constipation and abdominal pain.

**References:**