



BlueCross BlueShield  
of Alabama

## **Amitiza<sup>®</sup> (lubiprostone), Linzess<sup>®</sup> (linaclotide), Trulance<sup>™</sup> (plecanatide) Prior Authorization Program Summary**

This prior authorization program applies to Commercial, GenPlus, SourceRx and Health Insurance Marketplace formularies.

### **OBJECTIVE**

The intent of the Prior Authorization (PA) program for Amitiza (lubiprostone), Linzess (linaclotide), and Trulance (plecanatide) is to ensure appropriate selection of patients for treatment according to product labeling and/or clinical studies and/or guidelines. The PA defines appropriate use as use in patients with a Food and Drug Administration (FDA) approved indication of chronic idiopathic constipation (in adults), irritable bowel syndrome with constipation (Amitiza and Linzess only), or opioid-induced constipation in adults with chronic non-cancer pain (Amitiza only). The PA criteria require that the patient has had symptoms of chronic idiopathic constipation or irritable bowel syndrome with constipation  $\geq 3$  months. The PA criteria also require that patients have tried at least two standard laxative therapy classes for constipation, including osmotic laxatives (polyethylene glycol, lactulose, magnesium hydroxide-based including milk of magnesia), fiber or bulking agents (psyllium, bran, methylcellulose), stool softeners (docusate), or over-the-counter stimulant laxatives containing senna or bisacodyl. Criteria do not allow coverage in patients who have FDA labeled contraindication(s) to the requested product. Requests will be reviewed when patient-specific documentation has been provided.

### **TARGET AGENTS**

**Amitiza** (lubiprostone)

**Linzess** (linaclotide)

**Trulance** (plecanatide)

### **PRIOR AUTHORIZATION CRITERIA FOR APPROVAL**

**Amitiza** will be approved when ALL of the following are met:

1. ONE of the following:
  - a. The patient is  $\geq 18$  years of age with a diagnosis of irritable bowel syndrome with constipation with documentation of symptoms for  $\geq 3$  months **AND** ONE of the following:
    - i. The patient is female

**OR**

  - ii. The prescriber has provided documentation that the requested agent is medically appropriate for the patient's gender and the intended diagnosis
- OR**

b. The patient is  $\geq 18$  years of age with a diagnosis of chronic idiopathic constipation with documentation of symptoms for  $\geq 3$  months
- OR**

c. The patient is  $\geq 18$  years of age with a diagnosis of opioid-induced constipation with chronic non-cancer pain **AND** ALL of the following:

- i. The patient has chronic use of an opioid agent in the past 30 days
  - AND**
  - ii. The patient is not currently receiving a diphenylheptane opioid (e.g. methadone)
- AND**
- 2. ONE of the following:
    - a. The patient has tried at least 2 standard laxative therapy classes
  - OR**
  - b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to at least 2 standard laxative therapy classes
- AND**
- 3. The patient does NOT have any FDA labeled contraindication(s) to the requested agent

**Length of approval:** 12 months

**Linzess** will be approved when ALL of the following are met:

- 1. ONE of the following:
    - a. The patient is  $\geq 18$  years of age with a diagnosis of irritable bowel syndrome with constipation with documentation of symptoms for  $\geq 3$  months
  - OR**
  - b. The patient is  $\geq 18$  years of age with a diagnosis of chronic idiopathic constipation with documentation of symptoms for  $\geq 3$  months
- AND**
- 2. ONE of the following:
    - a. The patient has tried at least 2 standard laxative therapy classes
  - OR**
  - b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to at least 2 standard laxative therapy classes
- AND**
- 3. The patient does NOT have any FDA labeled contraindication(s) to the requested agent

**Length of approval:** 12 months

**Trulance** will be approved when ALL of the following are met:

- 1. ONE of the following:
    - a. The patient is  $\geq 18$  years of age with a diagnosis of chronic idiopathic constipation with documentation of symptoms for  $\geq 3$  months
  - OR**
  - b. The patient is  $\geq 18$  years of age with a diagnosis of irritable bowel syndrome with constipation with documentation of symptom for  $\geq 3$  months
- AND**
- 2. ONE of the following:
    - a. The patient has tried at least 2 standard laxative therapy classes
  - OR**
  - b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to at least 2 standard laxative therapy classes
- AND**
- 3. The patient does NOT have any FDA labeled contraindication(s) to the requested agent

**Length of approval:** 12 months

*on (i) information in FDA approved package inserts (and black box warning, alerts, or other information disseminated by the FDA as applicable); (ii) research of current medical and pharmacy literature; and/or (iii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.*

*The purpose of Blue Cross and Blue Shield of Alabama's pharmacy policies are to provide a guide to coverage. Pharmacy policies are not intended to dictate to physicians how to practice medicine. Physicians should exercise their medical judgment in providing the care they feel is most appropriate for their patients.*

*Neither this policy, nor the successful adjudication of a pharmacy claim, is guarantee of payment.*

**FDA APPROVED INDICATIONS AND DOSAGE<sup>1,3,13</sup>**

<b>Agent</b>	<b>Indication(s)</b>	<b>Dosage and Administration</b>
<p><b>Amitiza</b> (lubiprostone)</p> <p>capsules (8 mcg, 24 mcg)</p>	<p>Treatment of irritable bowel syndrome with constipation (IBS-C) in women <math>\geq</math> 18 years old.</p> <p>Treatment of chronic idiopathic constipation (CIC) in adults.</p> <p>Treatment of opioid-induced constipation (OIC) in adults with chronic, non-cancer pain. Limitation of Use: Effectiveness of Amitiza in the treatment of OIC in patients taking diphenylheptane opioids (e.g. methadone) has not been established.</p>	<p><b>IBS-C-</b> 8 mcg taken twice daily orally with food and water.</p> <p><b>CIC, OIC -</b> 24 mcg taken twice daily orally with food and water.</p> <p>For patients with moderately impaired hepatic function (Child-Pugh Class B), recommended starting dose is 16 mcg twice daily; for patients with severely impaired hepatic function (Child-Pugh Class C), recommended starting dose is 8 mcg twice daily. If tolerated dose can be escalated if needed.</p>
<p><b>Linzess</b> (linaclotide)</p> <p>capsules (72 mcg, 145 mcg, 290 mcg)</p>	<p>Treatment of irritable bowel syndrome with constipation (IBS-C) in adults.</p> <p>Treatment of chronic idiopathic constipation (CIC) in adults.</p>	<p><b>IBS-C-</b> 290 mcg taken once daily orally on an empty stomach, at least 30 minutes prior to the first meal of the day.</p> <p><b>CIC-</b> 145 mcg orally once daily or 72 mcg orally once daily based on individual presentation or tolerability, at least 30 minutes prior to the first meal of the day.</p>
<p><b>Trulance</b> (plecanatide)</p> <p>tablets (3 mg)</p>	<p>Treatment of chronic idiopathic constipation (CIC) in adults.</p> <p>Treatment of irritable bowel syndrome with constipation (IBS-C) in adults</p>	<p><b>CIC/IBS-C -</b>The recommended adult dosage is 3 mg taken orally once daily.</p>

**CLINICAL RATIONALE**

**Chronic Idiopathic Constipation (CIC):**

Rome IV diagnostic criteria for functional constipation requires the presence of the following for at least 3 months:<sup>16</sup>

- Must include two or more of the following:
  - Straining during more than 25 percent of defecations
  - Lumpy or hard stools (Bristol Stool Scale Form 1-2) in more than 25 percent of defecations
  - Sensation of incomplete evacuation for more than 25 percent of defecations
  - Manual maneuvers to facilitate more than 25 percent of defecations (e.g., digital evacuation, support of the pelvic floor)
  - Fewer than three spontaneous bowel movements per week
- Loose stools are rarely present without the use of laxatives
- There are insufficient criteria for Irritable Bowel Syndrome (IBS)

The American College of Gastroenterology (ACG) (2014) states that although linaclotide and lubiprostone are effective in CIC and are well tolerated, there have been no comparative studies. As both were evaluated in comparison with placebo rather than “standard therapy,” a recommendation regarding their precise position in a CIC treatment algorithm (i.e., for those who have failed fiber, osmotic, or stimulant laxatives, or as primary therapy) cannot be made at this time.<sup>6</sup>

American Gastroenterology Association recommends a gradual increase in fiber intake, as both foods included in the diet and as supplements and/or an inexpensive osmotic agent (e.g., milk of magnesia or polyethylene glycol). Depending on stool consistency, the next step may be to supplement the osmotic agent with a stimulant laxative (e.g., bisacodyl or glycerol suppositories), preferably administered 30 minutes after a meal to synergize the pharmacologic agent with the gastrocolonic response. A newer agent (e.g., lincosotide, lubiprostone, etc) should be considered when symptoms do not respond to other laxatives.<sup>15</sup>

UpToDate states that for initial management, suggest dietary fiber and bulk-forming laxatives (e.g., psyllium or methylcellulose), together with adequate fluids. For patients who do not tolerate bulk-forming laxatives or respond poorly to fiber, suggest an osmotic laxative next if tolerated. Other options include stool softeners, stimulant laxatives (bisacodyl, senna, and sodium picosulfate), and secretory agents (lubiprostone, linaclotide, plecanatide).<sup>14</sup>

### **Irritable Bowel Syndrome with Constipation (IBS-C):**

Rome IV defines IBS as recurrent abdominal pain, on average, at least one day per week in the last three months associated with two or more of the following:<sup>17</sup>

- Related to defecation
- Associated with a change in stool frequency
- Associated with a change in stool form (appearance)

The goal of treatment of IBS-C is to improve symptoms such as abdominal bloating, discomfort, and constipation. The American College of Gastroenterology states that in some patients, lifestyle modifications, high fiber diets, over-the-counter laxatives (including bulking agents such as psyllium and polyethylene glycol [PEG]), tricyclic antidepressants and SSRIs, or antispasmodics may be effective treatment. In more severe cases of IBS-C, lubiprostone may be effective.<sup>2</sup> The guideline states that lubiprostone has not been studied in men and that more data is needed before lubiprostone can be recommended in men with IBS-C.<sup>2</sup>

The American College of Gastroenterology monograph (2014) on the management of IBS and CIC states that although linaclotide and lubiprostone are effective in constipation-predominant IBS, these agents were evaluated vs. placebo rather than “standard therapy”. Their position in an IBS treatment algorithm (i.e., for those who have failed other treatments or as primary therapy) is difficult to define and complicated by lack of consensus on what “standard” therapy should be in IBS, given the limitations of data on other agents.<sup>6</sup>

A review (2015) states relatively small response rates, higher costs, and adverse effects associated with lubiprostone and linaclotide will likely render these agents suitable as second-line therapies in the treatment of IBS-C and CIC.<sup>10</sup>

The National Institute for Health and Care Excellence (NICE, UK, 2015) guidelines on treatment of IBS suggest to consider linaclotide for people with IBS only if optimal or maximum tolerated doses of laxatives from different classes have not helped and the person has had constipation for at least 12 months. Lubiprostone is licensed for chronic idiopathic constipation “when lifestyle changes are inadequate”. However no recommendation was made owing to a lack of quality evidence on effectiveness.<sup>11</sup>

The World Gastroenterology Organization (2015) states there is no general agreement on the cause of IBS, and no single treatment is currently regarded throughout the world as being universally applicable to the management of all IBS patients. Lubiprostone and linaclotide are considered safe and effective for treatment of IBS-C. However, nausea has been the major side effect limiting use of lubiprostone. Diarrhea is the major adverse effect of linaclotide; and further studies are needed to evaluate its long-term efficacy and safety.<sup>12</sup>

### **Opioid-Induced Constipation (OIC):**

There is no single definition of OIC. In clinical trials of lubiprostone, inclusion criteria for OIC were defined as "the occurrence of either less than 3 spontaneous bowel movements (SBMs) per week, with at least 25% of SBMs associated with one or more of the following conditions: hard to very hard stool consistency; moderate to very severe straining; and/or having a sensation of incomplete evacuation."<sup>1</sup> Oral laxatives are the mainstay of the treatment of OIC, classified into two general categories, softening (i.e., docusate) and peristalsis-inducing agents (i.e., senna and bisacodyl). These agents are non-specific, as they do not affect the opioid receptor-mediated reason for constipation.<sup>4</sup>

A treatment pathway for OIC (2014, U.K.) first recommends non-pharmacologic intervention (increased fluids, fiber, and physical activity), and then laxative intervention (e.g., stimulants, softeners, enemas, etc) on starting opioid use and for the duration of treatment, followed by use of opioid antagonists as the last step in the pathway.<sup>7</sup>

A review on OIC (2013, U.S.) suggests stimulant laxatives, with or without stool softeners, as the first-line pharmacologic treatment used in most patients. Only 50 % of patients experience satisfactory relief using this strategy. For this reason, treatment with laxatives often requires frequent dose adjustments, combination therapy, and laxative switching before achieving satisfactory results. Unfortunately, these agents rarely provide complete relief from OIC. In resistant patients, opioid rotation, and agents such as lubiprostone, and methylnaltrexone should be considered.<sup>8</sup>

OIC Consensus Recommendations (2015): In anticipation of potential OIC development with long-term opioid use, treatment guidelines recommend initiation of a prophylactic bowel regimen that may involve increased fluid and fiber intake, stool softeners, and/or laxatives. When a diagnosis of OIC is suspected despite prophylactic treatment, clinicians should confirm that initiation of opioid therapy has led to a change from baseline in the patient's typical bowel habits, before consideration of further or alternative interventions. First line approaches to intervention also include dietary changes, OTC treatments, and exercise. The panel believes that the accessibility and relatively low risk of dietary and OTC options justify their prophylactic and first-line use for OIC.<sup>9</sup>

National Comprehensive Cancer Network (NCCN, 2017) guidelines on adult cancer pain include the following recommendations on OIC. Preventative measures include prophylactic medications (stimulant laxative, polyethylene glycol), maintaining adequate fluid intake, maintaining adequate dietary fiber, and exercise if feasible. Supplemental medicinal fiber is unlikely to control OIC and may worsen constipation. Docusate may not provide benefit. If constipation develops, titrate stool softeners/laxatives as needed to achieve one non-forced bowel movement every 1-2 days. Consider adjuvant analgesics to allow reduction of opioid dose. If constipation persists, consider adding another agent (magnesium hydroxide, bisacodyl, lactulose, sorbitol, magnesium citrate, polyethylene glycol). When response to laxative therapy has not been sufficient for OIC in patients with advanced illness, then consider methylnaltrexone or naloxegol; other second line agents include lubiprostone and linaclotide.<sup>5</sup>

### **Safety**

Linaclotide carries a black box warning that it is contraindicated in pediatric patients up to 6 years of age. Linaclotide caused deaths due to dehydration in young juvenile mice. Avoid use of linaclotide in pediatric patients 6 through 17 years of age. The safety and efficacy of linaclotide has not been established in pediatric patients under 18 years of age. It also carries an additional contraindication in patients with known or suspected mechanical gastrointestinal obstruction.<sup>3</sup>

Lubiprostone is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.<sup>1</sup>

Plecanatide is contraindicated in patients less than 6 years of age due to the risk of serious dehydration and also in patients with known or suspected mechanical gastrointestinal obstruction.<sup>13</sup>

Plecanatide carries the following black box warnings:<sup>13</sup>

- Plecanatide is contraindicated in patients less than 6 years of age; in young juvenile mice, plecanatide caused death due to dehydration.
- Avoid use of plecanatide in patients 6 years to less than 18 years of age.
- The safety and effectiveness of plecanatide have not been established in patients less than 18 years of age.

For additional clinical information see the Prime Therapeutics Formulary Chapters 7.1: Laxatives and 7.7E: Irritable Bowel Syndrome Agents and Formulary Monograph: Linaclotide.

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*This pharmacy policy is not an authorization, certification, explanation of benefits or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All pharmacy policies are based on (i) information in FDA approved package inserts (and black box warning, alerts, or other information disseminated by the FDA as applicable); (ii) research of current medical and pharmacy literature; and/or (iii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.*

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