Opioid-Induced Constipation Agents

EOCCO POLICY

Policy Type: PA Pharmacy Coverage Policy: EOCCO144

Description

Methylnaltrexone bromide (Relistor), naldemedine (Symproic), and naloxegol (Movantik) are orally administered mu-opioid antagonists that act specifically in the peripheral tissues with inhibited central nervous system penetration at recommended dosages.

Length of Authorization

- Initial: Three months
- Renewal: 6 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
methylnaltrexone bromide (Relistor)	150 mg tablets	Treatment of opioid-induced constipation in adults with chronic non-cancer pain	90 tablets/30 days
	12 mg vial/syringe	Treatment of opioid-induced constipation with advanced illness or pain caused by active cancer requiring opioid dosage escalation	30 single use vials or syringes/30 days
	8 mg vial/syringe		30 single use vials or syringes/30 days
naldemedine (Symproic)	0.2 mg tablets	Treatment of opioid-induced constipation in adults with chronic non-cancer pain	30 tablets/30 days
naloxegol (Movantik)	12.5 mg tablets		30 tablets/30 days
	25 mg tablets		30 tablets/30 days

Initial Evaluation*

* Methylnaltrexone bromide (Relistor), naldemedine (Symproic), and naloxegol (Movantik) are medications used to treat constipation, a non-funded condition according to the Oregon Health Plan Prioritized List of Healthcare Services.

Constipation falls under non-covered line 526. Treatment with opioids for chronic pain under a covered line allows for these therapies to be covered. Examples of covered lines that require chronic opioids include: conditions of the back and spine, a covered cancer diagnosis, fractures, etc.

If the condition becomes a covered line according to the Oregon Health Plan Prioritized List of Healthcare Services, the following applies:

I. Methylnaltrexone bromide (Relistor), naldemedine (Symproic), and naloxegol (Movantik) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Diagnosis of **Opioid-Induced Constipation (OIC)** when the following are met:
      1. Treatment with the following has been ineffective, contraindicated, or not tolerated:
         i. Two different types of agents from the following OTC laxatives:
            a. Stool softener (e.g. docusate sodium); **OR**
            b. Osmotic agent (e.g. polyethylene glycol); **OR**
            c. Stimulant laxative (e.g. sennoside); **OR**
            d. Other; **AND**
         ii. If the request is for methylnaltrexone bromide (Relistor):
            a. Treatment with all of the following has been ineffective, contraindicated, or not tolerated:
               i. naloxegol (Movantik); **AND**
               ii. naldemedine (Symproic)

II. Methylnaltrexone (Relistor), naldemedine (Symproic) and naloxegol (Movantik) are considered investigational when used for all other conditions, including but not limited to:
   A. Constipation not induced by opioids
   B. Post-operative ileus

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise; **AND**
III. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
IV. Member is continuing to receive chronic opioids; **AND**
V. Member has shown an improvement in the number of bowel movements they are having

Supporting Evidence

I. The American Gastroenterological Association (AGA) guidelines recommend the use of naloxegol (Movantik) and naldemedine (Symproic) for laxative-resistant patients with OIC. Methylnaltrexone bromide (Relistor) was given a conditional recommendation for laxative-resistant patients with OIC as the evidence was considered low quality. The AGA did not make a recommendation for lubriprostone (Amitiza®) as the evidence was low quality and inconsistent, with one trial not showing any statistical difference from placebo.

II. Methylnaltrexone bromide (Relistor) was studied in four trials compared against placebo. Patients were not on any background therapies in studies one and two. Studies four and five allowed patients to continue on their regular laxative regimen. The evidence is considered low quality with some studies having high rates of dropout and endpoints evaluated in studies four and five having unknown clinical benefit for patients.

- Study one and two were randomized, double-blind, placebo-controlled trials evaluating 713 patients with OIC and chronic non-cancer pain. Methylnaltrexone bromide (Relistor) tablets and injection demonstrated a statistically significant response for proportion of responders compared to placebo. The percent difference was 13% (CI 3%, 23%) for study one and 20% (CI 10%, 31%) for study two.
- Study three was a long-term, open-label, uncontrolled trial looking at 1,034 patients with OIC and chronic non-cancer pain. Safety was the primary endpoint with the most common adverse events being abdominal pain, diarrhea, nausea, and psychiatric disorders. The mean change in bowel movements from baseline was 1.5 bowel movements per week ($p<0.001$).
- Study four and five were double-blind, placebo-controlled trials evaluating 287 patients with OIC and advanced illness (patients receiving palliative opioid therapy). Methylnaltrexone bromide (Relistor) injection demonstrated a statistically significant improvement in the proportion of patients with a rescue-free laxation within four hours of study medication compared to placebo. Results from study four were 62%, 58%, 14% ($p<0.0001$) for the 0.15 mg/kg dose, 0.3 mg/kg dose, and placebo, respectively, and study five results were 48% and 16% ($p<0.0001$) for methylnaltrexone bromide (Relistor) and placebo, respectively.

III. Naloxegol (Movantik) was studied in two randomized, double-blind, placebo-controlled trials in patients with OIC and chronic non-cancer pain. The primary endpoint for both studies evaluated response to therapy defined as ≥3 spontaneous bowel movements (SBMs) per week and a change from baseline of ≥1 SBM per week for at least nine out of the 12 study weeks and three out of the last four study weeks.

- Study one and two evaluated 1,352 patients comparing 12.5 mg and 25 mg of naloxegol (Movantik) against placebo. There was a statistically significant difference for both strengths compared to placebo in study one and only the 25 mg strength in

study two. A treatment difference of 11.4% (2.4%, 20.4%) and 15% (5.9%, 24%) for 12.5 mg and 25 mg, respectively, was seen in study one and 10.3% (1.7%, 18.9%) in study two.

IV. Naldemedine (Symproic) was studied in four randomized, double-blind, placebo-controlled trials looking at patients with OIC and chronic non-cancer pain. The primary endpoint for both studies evaluated response to therapy defined as ≥3 SBMs per week and a change from baseline of ≥1 SBM per week for at least nine out of the 12 study weeks and three out of the last four study weeks.

- Study one and two were 12 week trials evaluating 1,080 patients comparing 0.2 mg of naldemedine (Symproic) against placebo. There was a statistically significant difference for naldemedine (Symproic) compared to placebo with a treatment difference of 13% (CI 5%, 21%) for study one and 19% (CI 11%, 27%) for study two.
- Study three was a 52 week trial evaluating 1246 patients comparing 0.2 mg of naldemedine (Symproic) against placebo. The primary outcome measured was treatment emergent adverse events which did not have any difference between treatment arms. There was sustained improvement in bowel movement frequency for naldemedine (Symproic) compared to placebo ~3.5 vs ~2.5, respectively ($p<0.0001$).
- Naldemedine (Symproic) was compared against placebo in a two week, randomized, double-blind, placebo-controlled trial with an open-label 12 week extension evaluating 193 patients with active cancer. Naldemedine (Symproic) had a statistically significant difference over placebo for the primary endpoint of proportion of SBM responders with a treatment difference of 36.8% (CI 23.7%, 49.9%).

Investigational or Not Medically Necessary Uses

I. These therapies have not been studied in the following conditions:
   A. Constipation not induced by opioids
   B. Post-operative Ileus

References

1. Relistor [Prescribing Information]. Bridgewater, NJ: Salix Pharmaceuticals, Inc. November 2018.
2. Movantik [Prescribing Information]. Wilmington, DE: AstraZeneca Pharmaceuticals. May 2019.
3. Symproic [Prescribing Information]. Raleigh, NC: BioDelivery Sciences International, Inc. April 2019.
4. Uptodate, Inc. Prevention and management of side effects in patients receiving opioids for chronic pain [database online]. Waltham, MA. Updated 11/11/19. Available at: http://www.uptodate.com/home/index.html. [Accessed 11/19/19].
5. Crockett SD, Greer KB, Heidelbaugh JJ, Falck-Ytter Y, Hanson BJ, Sultan S. American Gastroenterological Association Institute Guideline on the Medical Management of Opioid-Induced Constipation. *Gastroenterology*. 2019;156(1):218-226.

6. Webster LR, Michna E, Khan A, Israel RJ, Harper JR. Long-Term Safety and Efficacy of Subcutaneous Methylnaltrexone in Patients with Opioid-Induced Constipation and Chronic Noncancer Pain: A Phase 3, Open-Label Trial. *Pain Med*. 2017;18(8):1496-1504.
7. Webster LR, Nalamachu S, Morlion B, et al. Long-term use of naldemedine in the treatment of opioid-induced constipation in patients with chronic noncancer pain: a randomized, double-blind, placebo-controlled phase 3 study. *Pain*. 2018;159(5):987-994.
8. Katakami N, Harada T, Murata T, et al. Randomized Phase III and Extension Studies of Naldemedine in Patients With Opioid-Induced Constipation and Cancer. *J Clin Oncol*. 2017;35(34):3859-3866.

Policy Implementation/Update:

Date Created	January 2018
Date Effective	February 2018
Last Updated	March 2018
Last Reviewed	03/2018

Action and Summary of Changes	Date
Transitioned criteria to policy: removed required trial and failure of lubiprostone (Amitiza) for all agents	11/2019