Pharmacy Benefit Coverage Criteria

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Coverage Policy Number ............................ P0091

Opioid Induced Constipation

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Related Coverage Resources

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer’s particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer’s benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer’s benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Medical Necessity Criteria

Products for opioid induced constipation include the following:

- **Relistor**® (methylnaltrexone bromide)
- **Movantik**® (naloxegol)
- **Symproic**® (naldemidine)

*Amitiza (lubiprostone) is FDA approved for treatment of opioid induced constipation but is not subject to prior authorization.

Relistor Tablet (methylnaltrexone bromide), Movantik (naloxegol), Symproic (naldemidine) are considered medically necessary when ALL of the following criteria are met:

- Age 18 years of age and older
- Diagnosis of opioid-induced constipation (OIC)
- Documentation of chronic opioid use not requiring frequent (for example, weekly) opioid dosage escalation
- Individual has had an inadequate laxative response for a minimum of 4 days within a 2 week period (for example: lactulose, bisacodyl)
Relistor® Injection (methylnaltrexone bromide) is considered medically necessary when ALL of the following criteria are met:

- Age 18 years of age and older
- Diagnosis of opioid-induced constipation (OIC)
- **ONE of the following:**
  - Documentation of chronic opioid use not requiring frequent (for example, weekly) opioid dosage escalation
  - Advanced illness or pain caused by active cancer requiring opioid dosage escalation for palliative care
- Individual has had an inadequate laxative response for a minimum of 4 days within a 2 week period (for example: lactulose, bisacodyl)

Initial authorization is up to 12 months.

Relistor (methylnaltrexone bromide), Movantik (naloxegol), and Symproic (naldemidine) are considered medically necessary for continued use when the initial criteria are met.

Reauthorization for up to 12 months.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Movantik, Relistor, and Symproic are considered experimental, investigational or unproven for ANY other use.

Note: Receipt of sample product does not satisfy any criteria requirements for coverage.

### FDA Approved Indications

<table>
<thead>
<tr>
<th>Product</th>
<th>FDA Approved Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Movantik (naloxegol)</td>
<td>Movantik is indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (e.g., weekly) opioid dosage escalation.</td>
</tr>
<tr>
<td>Relistor (methylnaltrexone bromide)</td>
<td>Opioid-Induced Constipation in Adult Patients with Chronic Non-Cancer Pain Relistor tablets and Relistor injection are indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (e.g., weekly) opioid dosage escalation. Opioid-Induced Constipation in Adult Patients with Advanced Illness Relistor injection is indicated for the treatment of OIC in adult patients with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care.</td>
</tr>
<tr>
<td>Symproic (naldemedine)</td>
<td>Symproic is indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (e.g., weekly) opioid dosage escalation.</td>
</tr>
</tbody>
</table>

### Recommended Dosing

**FDA Recommended Dosing**
Pharmacy Benefit Clinical Criteria: P0091

**Movantik (naloxegol)**
The recommended Movantik dosage is 25 mg once daily in the morning. If patients are not able to tolerate Movantik, reduce the dosage to 12.5 mg once daily [see Clinical Pharmacology (12.2)].

**Relistor (methylnaltrexone bromide)**
Opioid-Induced Constipation in Adult Patients with Chronic Non-Cancer Pain
- The recommended dosage of Relistor tablets is 450 mg taken orally once daily in the morning.
- The recommended dosage of Relistor injection is 12 mg administered subcutaneously once daily.

Opioid-Induced Constipation in Adult Patients with Advanced Illness
The pre-filled syringe is only for patients who require a Relistor injection dose of 8 mg or 12 mg. Use the vial for patients who require other doses of Relistor injection.

The table below shows the recommended weight-based dose of Relistor injection and the corresponding injection volume. The recommended dosage regimen is one dose administered subcutaneously every other day, as needed. Do not administer more frequently than one dose per 24-hour period.

<table>
<thead>
<tr>
<th>Weight of Adult Patient</th>
<th>Subcutaneous Dose</th>
<th>Injection Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 38 kg</td>
<td>0.15 mg/kg</td>
<td>See below*</td>
</tr>
<tr>
<td>38 kg to less than 62 kg</td>
<td>8 mg</td>
<td>0.4 mL</td>
</tr>
<tr>
<td>62 kg to 114 kg</td>
<td>12 mg</td>
<td>0.6 mL</td>
</tr>
<tr>
<td>More than 114 kg</td>
<td>0.15 mg/kg</td>
<td>See below*</td>
</tr>
</tbody>
</table>

* Calculate the injection volume for these patients by multiplying the patient weight in kilograms by 0.0075 and then rounding up the volume to the nearest 0.1 mL.

**Symproic (naldemedine)**
The recommended dosage of Symproic is 0.2 mg orally once daily with or without food.

**Background**

**Professional Societies/Organizations**
**American Gastroenterological Association (AGA)**
Opioid induced bowel dysfunction, per the AGA, refers to gastrointestinal adverse effects associated with opioid therapy, which may consist of: constipation, gastroesophageal reflux disease, nausea and vomiting, bloating, and abdominal pain. The term opioid-induced constipation refers to constipation that resulting from therapy with opioids. OIC is defined by a consensus as “a change when initiating opioid therapy from baseline bowel habits that is characterized by any of the following: reduced bowel movement frequency, development or worsening of straining to pass bowel movements, a sense of incomplete rectal evacuation, or harder stool frequency. OIC, though, is defined variably in the literature and some studies do not include a specific definition. OIC is estimated to affect 40%-80% of patients taking chronic opioid therapy. Laxative-refractory OIC has been variably defined in the literature as moderate or severe symptoms of constipation, despite the use of laxatives from 1 or more laxative classes for a minimum of 4 days within a 2-week period. AGA recommends, for first line treatment, laxatives. For patients that have laxative refractory OIC, naldemedine or naloxegol are recommended over the use of no treatment. In addition, methylnaltrexone is suggested over no treatment. The AGA guideline does not make recommendations relating to the use of lubiprostone or prucalopride for OIC due to lack of evidence. (Crockett, 2019)

The American Board of Internal Medicine’s (ABIM) Foundation Choosing Wisely® Initiative:
No recommendations are available for Opioid Induced Constipation Agents.

**Centers for Medicare & Medicaid Services - National Coverage Determinations (NCDs)**
There are no CMS National Coverage Determinations for Opioid Induced Constipation Agents.

**Other Covered Uses**

**Opioid Induced Constipation in Cancer**

The National Comprehensive Care Network (NCCN) Palliative Care guidelines (version 2.2019) states that peripherally acting mu opioid receptor antagonists (PAMORAs) may help to relieve OIC while also maintaining the management of pain. Recent studies with methylnaltrexone have shown effective relief of OIC while still preserving opioid mediated analgesia in the patient. Also Naloxegol has been studied for treating OIC in noncancer pain patients on chronic opioids. Based on these studies, the NCCN panel recommends methylnaltrexone every other day (no more than once per day) of 0.15 mg per kilogram body weight for those who have not responded to laxatives. NCCN guidelines for palliative care recommends for opioid induced constipation methylnaltrexone, 8 or 12 mg/dose subcutaneous, no more than once per day; linaclotide, m 72 – 145 mcg/day orally, or naloxegol, 12.5-12mg/day orally. It should not be used in patients with a postoperative ileus or mechanical bowel obstruction. (NCCN, 2019)

In addition, COMPOSE 4 was a two week randomized, double blind, placebo controlled trial that examined naldemedine 0.2 mg in patients with OIC and cancer and COMPOSE 5, an open label extension study, was a 12-week study. In COMPOSE 4, adults with OIC and cancer were randomly assigned on a 1:1 basis to receive once-daily oral naldemedine 0.2 mg or placebo. A greater change from baseline was observed with naldemedine compared to placebo in the frequency of spontaneous bowel movements (SBMs) per week, SBMs with complete bowel evacuation/week, and SBMs without straining/week. Naldemedine was not associated with symptoms of opioid withdrawal and also had no observable impact on opioid-mediated analgesia. (Katakami, 2017)

**References**

1. AHFS Drug Information 2019

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