Opioid Induced Constipation (OIC) Prior Authorization Program Summary

This program applies to FlexRx Open, FlexRx Closed, GenRx Open, GenRx Closed, Medicaid, and Health Insurance Marketplace formularies.

This is a FlexRx standard and GenRx standard prior authorization.

The BCBS MN Step Therapy Supplement also applies to this program for all Commercial/HIM lines of business

**FDA APPROVED INDICATIONS AND DOSAGE**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication</th>
<th>Dosage &amp; Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relistor® (methylnaltrexone)</strong></td>
<td>Injection/Tablet: 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>
<td>12 mg SQ once daily 450 mg orally once daily</td>
</tr>
<tr>
<td>Subcutaneous injection (SQ)</td>
<td></td>
<td>Patients receiving opioids for less than 4 weeks may be less responsive to Relistor. Discontinue maintenance laxative therapy before starting Relistor; may resume laxatives if patients have OIC symptoms after taking Relistor for 3 days. Discontinue if treatment with opioid pain medication is also discontinued.</td>
</tr>
<tr>
<td>Tablet</td>
<td>Injection: Treatment of OIC in adult patients with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care</td>
<td>Once daily weight based administration every other day, as needed, but no more frequently than one dose in a 24 hour period</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adult Patient Weight</th>
<th>SQ dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;38 kg</td>
<td>0.15 mg/kg</td>
</tr>
<tr>
<td>38 kg to &lt;62 kg</td>
<td>8 mg</td>
</tr>
<tr>
<td>62 kg to 114 kg</td>
<td>12 mg</td>
</tr>
<tr>
<td>&gt;114 kg</td>
<td>0.15 mg/kg</td>
</tr>
</tbody>
</table>

Patients receiving opioids for less than 4 weeks may be less responsive to Relistor.

Discontinue maintenance laxative therapy before starting Relistor; may resume laxatives if patients have OIC symptoms after taking Relistor for 3 days.

Discontinue if treatment with opioid pain medication is also discontinued.
**Agent**

<table>
<thead>
<tr>
<th>Movantik™ (naloxegol)</th>
<th>Indication</th>
<th>Dosage &amp; Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>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>
<td>25 mg once daily; if not tolerated, reduce to 12.5 mg once daily</td>
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<tr>
<td></td>
<td></td>
<td>Renal Impairment (CrCl &lt; 60 mL/min): 12.5 mg once daily; increase to 25 mg once daily if tolerated and monitor for adverse reactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Discontinue maintenance laxative therapy before starting naloxegol; may resume laxatives if patients have OIC symptoms after taking naloxegol for 3 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients receiving opioids for less than 4 weeks may be less responsive to Movantik</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Discontinue if treatment with the opioid pain medication is also discontinued</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symproic® (naldemedine)</th>
<th>Indication</th>
<th>Dosage &amp; Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>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>
<td>0.2 mg once daily.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients receiving opioids for less than 4 weeks may be less responsive to Symproic.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Discontinue Symproic if treatment with the opioid pain medication is also discontinued.</td>
</tr>
</tbody>
</table>

**CLINICAL RATIONALE**

There is no single definition of OIC. In clinical trials of methylnaltrexone, inclusion criteria for OIC was defined as “the occurrence of either less than 3 bowel movements during the week or no significant laxation for 48 hours.” In clinical trials of naloxegol, OIC was defined as <3 spontaneous bowel movements (SBMs) per week on average with at least 25% of the SBMs associated with one or more of the following conditions: (1) straining, (2) hard or lumpy stools; and (3) a sensation of incomplete evacuation. 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.

A treatment pathway for OIC (2014, U.K.) first recommends nonpharmacologic 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.

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.\textsuperscript{7}

OIC Consensus Recommendation (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.\textsuperscript{8}

National Comprehensive Cancer Network (NCCN, 2018) 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.\textsuperscript{4}

### Safety\textsuperscript{1,5,9}

<table>
<thead>
<tr>
<th>Agent</th>
<th>Contraindication(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Movantik™</strong> (naloxegol)</td>
<td>Patients with known or suspected gastrointestinal obstruction and patients at increased risk of recurrent obstruction</td>
</tr>
<tr>
<td></td>
<td>Concomitant use with strong CYP3A4 inhibitors (e.g., clarithromycin, ketoconazole)</td>
</tr>
<tr>
<td></td>
<td>Known serious or severe hypersensitivity reaction to naloxegol or any of its excipients</td>
</tr>
<tr>
<td><strong>Relistor®</strong> (methylnaltrexone)</td>
<td>Patients with known or suspected mechanical gastrointestinal obstruction and at increased risk of recurrent obstruction</td>
</tr>
<tr>
<td><strong>Symproic®</strong> (naldemedine)</td>
<td>Patients with known or suspected gastrointestinal obstruction at increased risk of recurrent obstruction</td>
</tr>
<tr>
<td></td>
<td>Patients with a history of a hypersensitivity reaction to naldemedine.</td>
</tr>
</tbody>
</table>

For additional clinical information see the Prime Therapeutics Formulary Chapters 7.1: Laxatives.

### REFERENCES


Opioid Induced Constipation (OIC) Prior Authorization

OBJECTIVE
The intent of the prior authorization (PA) program for Opioid Induced Constipation (OIC) is to ensure appropriate selection of patients for treatment according to product labeling and/or clinical studies and/or guidelines. Target agents require either the trial of at least two traditional laxative therapy classes (stimulant laxatives, enemas, osmotic agents, or stool softeners) and received an inadequate response; or have a documented intolerance, FDA labeled contraindication, or hypersensitivity to two traditional laxative therapy classes. The criteria does not allow concomitant use of target agents. The criteria does not allow coverage in patients who have FDA labeled contraindications to the requested agent. Requests will be reviewed when patient-specific documentation has been provided.

TARGET AGENTS
Relistor® (methylnaltrexone)
Movantik™ (naloxegol)
Symproic® (naldemedine)

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Target Agent will be approved when ALL of the following are met:
1. ONE of the following:
   A. ALL of the following:
      i. The patient has a diagnosis of opioid induced constipation (OIC) and
         ONE of the following:
         1. The patient has advanced illness receiving palliative care OR pain
            caused by active cancer receiving palliative care; AND the
            requested agent is methylnaltrexone injection
            OR
         2. The patient has chronic non-cancer pain
            OR
         3. The patient has chronic pain related to prior cancer or its
            treatment
            OR
         4. The patient has active cancer pain AND the request is for Relistor
            (methylnaltrexone) OR Movantik (naloxegol)

AND
   ii. The patient has chronic use of an opioid agent in the past 30 days
AND
   iii. ONE of the following:
      1. The patient has tried and had an inadequate response to a
         minimum of two standard laxative therapy classes
         OR
      2. The patient has a documented intolerance, contraindication, or
         hypersensitivity to two standard laxative therapy classes
AND
   iv. ONE of the following:
      1. The patient is not taking another OIC opioid antagonist agent
         OR
      2. The other OIC opioid antagonist agent will be discontinued prior
         to starting the requested agent

OR
B. The patient has another FDA approved indication
AND
2. The patient does NOT have any FDA labeled contraindication(s) to the requested agent
Length of Approval: 12 months
Step Therapy Supplement

This program applies to FlexRx Closed, FlexRx Open, GenRx Closed, GenRx Open, Health Insurance Marketplace, FocusRx and KeyRx formularies.

Please note, this does not include or apply to quantity limit questions.

STEP THERAPY SUPPLEMENT

OBJECTIVE

The intent of the Step Therapy Supplement is to provide additional questions, to ensure compliance to MN Statute 62Q.184. These questions will apply if the step therapy component within a Prior Authorization or Step Therapy program is not able to be approved.

CONDITIONS FOR APPROVAL

The requested agent will be approved when ONE of the following are met:

1. The patient is currently being treated with the requested agent as indicated by ALL of the following:
   a. A statement by the prescriber that the patient is currently taking the requested agent
   AND
   b. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent
   AND
   c. The prescriber states that a change in therapy is expected to be ineffective or cause harm

   OR

2. The patient’s medication history include the required prerequisite/preferred agent(s) as indicated by:
   a. Evidence of a paid claim(s) within the past 999 days
   OR
   b. The prescriber has stated that the patient has tried the required prerequisite/preferred agent(s) in the past 999 days AND the required prerequisite/preferred agent(s) was discontinued due to lack of effectiveness or an adverse event

   OR

3. The prescriber has provided documentation that the required prerequisite/preferred agent(s) cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm

Length of Approval: As per program specific criteria