



## Opioid Induced Constipation (OIC) Prior Authorization Program Summary

This program applies to Commercial, Blue Partner, GenPlus, and Health Insurance Marketplace formularies.

### 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  
**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

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**FDA APPROVED INDICATIONS AND DOSAGE<sup>1,5,9</sup>**

FDA APPROVED INDICATIONS AND DOSAGE											
Agent	Indication	Dosage & Administration									
<b>Relistor®</b> (methylnaltrexone)  Subcutaneous injection (SQ)  Tablet	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	12 mg SQ once daily  450 mg orally once daily  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.									
	Injection: Treatment of OIC in adult patients with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care	Once daily weight based administration every other day, as needed, but no more frequently than one dose in a 24 hour period <table><tr><th>Adult Patient Weight</th><th>SQ dose</th></tr><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></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.	Adult Patient Weight	SQ dose	<38 kg	0.15 mg/kg	38 kg to <62 kg	8 mg	62 kg to 114 kg	12 mg	>114 kg
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<38 kg	0.15 mg/kg										
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>114 kg	0.15 mg/kg										
<b>Movantik™</b> (naloxegol)	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	25 mg once daily; if not tolerated, reduce to 12.5 mg once daily  Renal Impairment (CrCl < 60 mL/min): 12.5 mg once daily; increase to 25 mg once daily if tolerated and monitor for adverse reactions  Discontinue maintenance laxative therapy before starting naloxegol; may resume laxatives if patients have									

		<p>OIC symptoms after taking naloxegol for 3 days</p> <p>Patients receiving opioids for less than 4 weeks may be less responsive to Movantik</p> <p>Discontinue if treatment with the opioid pain medication is also discontinued</p>
<b>Symproic®</b> (naldemedine)	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.	<p>0.2 mg once daily.</p> <p>Patients receiving opioids for less than 4 weeks may be less responsive to Symproic.</p> <p>Discontinue Symproic if treatment with the opioid pain medication is also discontinued.</p>

## 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."<sup>2</sup> 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) have a sensation of incomplete evacuation.<sup>5</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.

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.<sup>6</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>7</sup>

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.<sup>8</sup>

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.<sup>4</sup>

#### **Safety<sup>1,5,9</sup>**

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

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

#### **REFERENCES**

1. Relistor Prescribing Information. Salix Pharmaceuticals. March 2018.
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6. Kumar L, Barker C, Emmanuel A. Review Article- Opioid-induced constipation: pathophysiology, clinical consequences, and management. *Gastroenterology Research and Practice*. 2014, Article ID 141737. Accessed at: <http://dx.doi.org/10.1155/2014/141737> .
7. Ketwaroo G, Cheng V, Lembo A. Opioid-induced bowel dysfunction. *Curr Gastroenterol Rep*. 2013;15:344: DOI 10.1007/s11894-013-0344-2.
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9. Symproic prescribing information. Purdue Pharma LP. January 2018.

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