Opioid Induced Constipation (OIC) Prior Authorization Criteria Program Summary

This program applies to Commercial 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. The PA defines appropriate use for methylnaltrexone as therapy of opioid-induced constipation (OIC) in patients with chronic non-cancer pain, or with advanced illness who are receiving palliative care. The PA defines appropriate use for naldemedine, naloxegol as therapy of OIC in patients with chronic non-cancer pain. Methylnaltrexone, naldemedine and naloxegol for the above indications require either the trial of at least two traditional laxative therapy classes (stimulant laxatives, enemas, osmotic agents, or stool softeners) or have a documented intolerance, FDA labeled contraindication, or hypersensitivity to two traditional laxative therapy classes. The criteria does not allow concomitant use of Relistor, Symproic and Movantik. 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 DRUG

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

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Opioid Induced Constipation 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 ONE of the following diagnoses:
            1. The patient has opioid induced constipation (OIC), and advanced illness and is receiving palliative care; AND the requested agent is methylnaltrexone
            OR
            2. The patient has OIC and chronic non-cancer pain

        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 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 opioid induced constipation opioid antagonist agent
            OR

2. The other opioid induced constipation 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[1,5,9]

<table>
<tr><th></th><th>Indication</th><th>Dosage & Administration</th></tr>
<tr><td>Relistor®
(methylnaltrexone)

Subcutaneous injection (SQ)

Tablet</td><td>Injection/Tablet:
Treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain

Injection:
Treatment of OIC in adult patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient. Use beyond 4 months has not been studied.</td><td>OIC induced constipation in adult patients with chronic non-cancer pain:
12 mg SQ once daily
450 mg orally once daily
Effectiveness has been shown in patients who have taken opioids for at least 4 weeks.
Discontinue maintenance laxative therapy before starting Relistor; may resume laxatives if patients have OIC symptoms after taking Relistor for 3 days.

OIC in adult patients with advanced illness:
Once daily weight based administration every other day, as needed, but no more frequently than one dose in a 24 hour period
<table>
<tr><td>Adult Patient Weight</td><td>SQ dose</td></tr>
<tr><td><38 kg</td><td>0.15 mg/kg</td></tr>
<tr><td>38 kg to <62 kg</td><td>8 mg</td></tr>
<tr><td>62 kg to 114 kg</td><td>12 mg</td></tr>
<tr><td>>114 kg</td><td>0.15 mg/kg</td></tr>
</table>
</td></tr>
<tr><td>Movantik™
(naloxegol)</td><td>Treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain</td><td>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 OIC symptoms after taking naloxegol for 3 days

Naloxegol has been shown to be efficacious in patients who have taken opioids for at least 4 weeks

Discontinue if treatment with the opioid pain medication is also discontinued</td></tr>
<tr><td>Symproic®
(naldemedine)</td><td>Treatment of opioid-induced constipation (OIC) in adult</td><td>0.2 mg once daily.</td></tr>
</table>

	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.	Patients receiving opioids for less than 4 weeks may be less responsive to Symproic. Discontinue Symproic if treatment with the opioid pain medication is also discontinued.

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."[2] 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.[5] 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.[6]

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.[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.[8]

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.[4]

Safety[1,5,9]

Agent	Contraindication(s)
Movantik™ (naloxegol)	Patients with known or suspected gastrointestinal obstruction and patients at increased risk of recurrent obstruction, due to the potential for gastrointestinal perforation Patients concomitantly using strong CYP3A4 inhibitors (e.g., clarithromycin, ketoconazole) because these medications can significantly increase exposure to naloxegol which may precipitate opioid withdrawal symptoms such as hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, irritability, and yawning Patients who have had a known serious or severe hypersensitivity reaction to naloxegol or any of its excipients
Relistor® (methylnaltrexone)	Patients with known or suspected gastrointestinal obstruction and patients at increased risk of recurrent obstruction, due to the potential for gastrointestinal perforation
Symproic® (naldemedine)	Patients with known or suspected gastrointestinal obstruction and patients at increased risk of recurrent obstruction, due to the potential for gastrointestinal perforation. Patients with a history of a hypersensitivity reaction to naldemedine. Reactions have included bronchospasm and rash.

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

REFERENCES

1. Relistor Prescribing Information. Salix Pharmaceuticals. May 2017.
2. FDA. Relistor NDA #0219964. *Clinical ph*armac*ology and biop*harmaceutics review (s) 3/11/2008.
3. Kurz A, *Sessler DI. Op*ioid-induced bowel dysfunction: pathophysiology and potential new therapies. *Drugs.* 2003;63:649–71.
4. National Comprehensive Cancer Network (NCCN) Clinical Practice guidelines in oncology. Adult Cancer Pain. Version. 2.2017. Accessed 6/15/2017.
5. Movantik prescribing information. Astra *Zeneca Pharmaceutical L*P. August 2016.
6. Kumar L, Barker C, Emmanuel A. Review Article- Opioid-induced constipation: pathophysiology, clinical consequences, and management. Gastroenterology R*esearch 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.
8. Argoff C, Brennan M, Camilleri M, et al. Review Article: Consensus recommendations on initiating prescription therapies for opioid-induced constipation. Pain Med. 2015;16(12):2324-2337.
9. Symproic prescribing information. Purdue Pharma LP. August 2017.

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