

Therapeutic Class Overview

Opioid-Induced Constipation Agents

Therapeutic Class Overview/Summary:

There are currently three agents approved by the Food and Drug Administration (FDA) for the treatment of opioid-induced constipation (OIC). Lubiprostone (Amitiza®), methylnaltrexone bromide (Relistor®), naloxegol oxalate (Movantik®) are indicated for the treatment of OIC in adults with chronic non-cancer pain. Additionally, methylnaltrexone bromide is also FDA-approved for use in adults with OIC who have advanced illness and are receiving palliative care.¹⁻³ While lubiprostone is also indicated for the treatment of chronic idiopathic constipation, and irritable bowel syndrome with constipation, those indications will not be covered in this review. Opioids are an effective and widely used treatment option to help control many different types of pain. Constipation, which can sometimes be severe, is a common side-effect of opioid use and may limit their acceptability.⁴ The cause of constipation associated with opioid use is thought to occur due to multiple etiologies. One factor is the ability of opioids to bind to the μ - and δ -opioid receptors found on smooth muscle within the gastrointestinal tract. This decreases peristalsis in the small intestine and colon by relaxing the intestinal smooth muscles and preventing normal bowel elimination functions. In addition, opioids are thought to interfere with normal fluid and electrolyte levels within the gastrointestinal lumen due to this longer gastrointestinal transit time that causes excessive water and electrolyte reabsorption from feces.⁵

Agents used for the treatment of OIC work via one of two mechanisms. Lubiprostone is a locally acting chloride channel activator that enhances a chloride-rich intestinal fluid secretion without altering sodium and potassium concentrations in the serum. Lubiprostone acts by specifically activating the chloride channel-2 (ClC-2), which is a normal constituent of the apical membrane of the human intestine. By increasing intestinal fluid secretion, lubiprostone increases motility of the intestine, thereby increasing the passage of stool and alleviating symptoms of constipation.¹ Methylnaltrexone bromide and naloxegol oxalate are selective μ -opioid antagonists that prevent the peripheral activation of μ -opioid receptors in certain tissues, such as the gastrointestinal tract, thus reducing the constipation side-effect. At therapeutic doses, neither agent interferes with the analgesic activity of opioids, which is caused by activation of μ -opioid receptors within the central nervous system (CNS).²⁻³ Methylnaltrexone bromide is a quaternary amine, which increases its polarity, and helps prevent its penetration into the CNS.² Naloxegol oxalate is a PEGylated derivative of naloxone, and is a substrate for the P-glycoprotein transporter (P-gp). The presence of a polyethylene glycol (PEG) moiety reduces its passive permeability into the CNS while being a substrate for P-gp increases efflux of naloxegol across the blood-brain barrier.³

Table 1. Current Medications Available in the Therapeutic Class¹⁻³

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Lubiprostone (Amitiza®)	Chronic Idiopathic constipation; opioid-induced constipation in chronic non-cancer pain, Irritable Bowel Syndrome with Constipation	Capsule: 8 μ g 24 μ g	-
Methylnaltrexone bromide (Relistor®)	Opioid-induced constipation in chronic non-cancer pain, Opioid-induced constipation in advanced illness	Prefilled Syringe: 8 mg/0.4 mL 12 mg/0.6 mL Vial, single-use: 12 mg/0.6 mL	-
Naloxegol oxalate (Movantik®)	Opioid-induced constipation in advanced illness	Tablet: 12.5 mg 25 mg	-

Evidence-based Medicine

- The efficacy of lubiprostone for the treatment of OIC was in patients receiving opioid therapy for chronic, non-cancer-related pain was assessed in three 12-week, randomized, double-blinded, placebo-controlled studies. In all three studies, patients had documented opioid-induced constipation at baseline, defined as having less than three spontaneous bowel movements (SBMs) per week, with at least 25% of SBMs associated with one or more of the following conditions: (1) hard to very hard stool consistency; (2) moderate to very severe straining; and/or (3) having a sensation of incomplete evacuation. Use of rescue laxatives was allowed in cases where no bowel movement had occurred in a 3-day period. At baseline, mean oral morphine equivalent daily doses (MEDDs) for the three studies were 99 mg and 130 mg, 237 mg and 265 mg, and 330 mg and 373 mg for placebo-treated and lubiprostone -treated patients, respectively.^{1,6,7} Studies one and two have been published, while study three remains unpublished. The primary endpoint of study one was the “overall responder” rate, defined as ≥ 1 SBM improvement over baseline frequency were reported for all treatment weeks for which data were available and ≥ 3 SBMs/week were reported for at least 9 of 12 treatment weeks. There was a statistically significant difference in favor of lubiprostone when compared to placebo for overall responder rate (27.1% compared with 18.9%; treatment difference, 8.2%; $P=0.030$). The primary endpoint of studies two and three was the mean change from baseline in SBM frequency at week eight. For study two, there was a statistically significant difference in changes from baseline in SBM frequency in favor of lubiprostone when compared to placebo (3.3 compared with 2.4; treatment difference, 0.9; $P=0.004$). However, in the unpublished study three, there was not a statistically significant difference in the mean change from baseline in SBM frequency at week eight between lubiprostone and placebo groups (2.7 compared to 2.5; treatment difference -0.2; $P=0.76$).¹
- The efficacy of methylnaltrexone bromide for the treatment of OIC was established in two clinical trials in patients with advanced illness receiving palliative care and one study in patients with chronic non-cancer pain.^{2,8,9} All studies were double-blind, placebo-controlled studies that compared methylnaltrexone 0.15 mg/kg and/or 0.3 mg/kg subcutaneously to placebo. The primary endpoint of the first study was the proportion of patients with a rescue-free laxation within four hours after a single dose of study medication or placebo. Methylnaltrexone bromide-treated patients had a significantly higher rate of laxation within four hours of the double-blind dose (62% for 0.15 mg/kg and 58% for 0.3 mg/kg) than did placebo-treated patients (14%); $P<0.0001$ for each dose compared with placebo.^{2,8} The second study evaluated the same primary end-point and found similar results. In this study the proportion of patients who had rescue-free laxation within four hours after receiving the first dose of the study drug was significantly higher in the methylnaltrexone bromide group than the placebo group (48% compared with 15%, respectively; $P<0.001$). In addition, the proportion of patients who had rescue-free laxation within four hours after receiving two or more of the first four doses was significantly higher in the methylnaltrexone bromide group compared to placebo (52% compared with 8%, respectively; $P<0.001$).^{2,9} The safety and efficacy of methylnaltrexone bromide for the treatment of OIC in patients with chronic non-cancer pain was evaluated in an unpublished study with results reported only in the FDA-approved package insert. The primary endpoint was the proportion of patients with greater than three spontaneous bowel movements (SBMs) per week during the four-week double-blind period. The results from this study showed that 59% of individuals in methylnaltrexone were found to have at least three SBMs per week compared to 38% in the placebo group ($P<0.001$).²
- The efficacy of naloxegol oxalate for the treatment of OIC in adults receiving opioids for chronic noncancer-related pain was evaluated in two phase III trials. Both studies were identically designed multicenter, randomized, double-blind, placebo-controlled, 12 week trials that evaluated naloxegol 12.5 mg and 25 mg compared to placebo. In both of the trials, the primary efficacy outcome was the rate of response over weeks one through 12 (defined as \geq SBMs/week and an increase from baseline of \geq one SBM per week for at least nine of 12 weeks and at least three out of the last four weeks). Results from these two studies revealed that naloxegol 25 mg provided a statistically significant improvement over placebo for the primary outcome ($P=0.001$ and $P=0.02$, respectively); however, naloxegol 12.5 mg showed statistical significance only in the first study ($P=0.02$ and $P=0.2$, respectively).^{3,10}

Key Points within the Medication Class

- There is limited current clinical guidance that address lubiprostone or the μ -opioid antagonists' place in therapy for OIC:^{5,11-14}
 - Most, existing guidelines were published prior to approval of these agents or are only briefly mentioned.¹²⁻¹⁴
 - Generally well-established bowel regimens are recommended for an initial case of OIC. This may include a scheduled dose of a stimulant laxative such, as bisacodyl or senna, with or without a stool-softener, such as docusate. Alternatively, daily administration of an osmotic laxative such as lactulose or polyethylene glycol may be used.^{5,11,12}
 - All laxatives are potential options and there is no data to suggest that any one approach is superior to any other.
 - The limited guidance that exists regarding the newer agents suggest that they are effective treatment options, but should be reserved for refractory cases of OIC only.^{5,11-14}
- Other Key Facts:
 - There are currently no generic products available.
 - Lubiprostone and naloxegol oxalate are available as oral dosage forms.

References

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