From The Medical Letter on Drugs and Therapeutics

# Naloxegol (Movantik) for Opioid-Induced Constipation

**The FDA has approved naloxegol** (Movantik – AstraZeneca), a pegylated derivative of the opioid antagonist naloxone, for oral treatment of opioid-induced constipation in adults with chronic noncancer pain. It is the only oral opioid antagonist approved for this indication in the US.

**Pronunciation Key**

Naloxegol: nal ox' ee gol  Movantik: mo van' tic

## Standard Treatment

Laxatives and stool softeners are commonly used, often in combination, for initial treatment of opioid-induced constipation, but their efficacy is limited. Methylnaltrexone (Relistor), a subcutaneously injected opioid antagonist, and lubiprostone (Amitiza), an oral chloride channel activator, are effective in increasing the frequency of bowel movements in patients with opioid-induced constipation and are FDA-approved for such use.[1-3] Alvimopan (Entereg), an oral mu-opioid receptor antagonist, has also been shown to be effective in patients with opioid-induced constipation, but it is approved only for short-term in-hospital treatment of postoperative ileus because of a possible risk of myocardial infarction with long-term use.[4]

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## Mechanism of Action

Opioids exert their analgesic effect by stimulating mu receptors in the central nervous system (CNS), but they also stimulate peripheral mu receptors in the gastrointestinal (GI) tract, leading to decreased muscle contractility, inhibition of water and electrolyte secretion, and increased rectal sphincter tone.[5] Naloxegol is a peripheral mu-opioid receptor antagonist (**Table 1**). Pegylation reduces the ability of naloxegol to cross the blood-brain barrier and makes it a substrate of the efflux transporter P-glycoprotein; these properties are thought to minimize its interference with opioid analgesic effects in the CNS.

## Clinical Studies

FDA approval of naloxegol was based on two identically designed 12-week trials in 652 and 700 patients with opioid-induced constipation who had been taking a stable dose of an oral opioid for noncancer pain.[6] Patients were randomized to once-daily treatment with naloxegol 12.5 or 25 mg or placebo. Response was defined as ≥3 spontaneous bowel movements (SBMs) per week for 12 weeks and an increase from baseline of at least 1 SBM per week for ≥9 of the 12 weeks and ≥3 of the final 4 weeks of the trial. Regular laxative use was prohibited during the trials.

Significantly more patients responded to naloxegol 25 mg than to placebo in both trials (44% and 40%, respectively, vs 29%). The response rate with the 12.5-mg dose was significantly higher than with placebo in the first trial, but not in the second (41% and 35% vs 29%). Prespecified subgroup analyses of patients who met criteria for an inadequate response to laxatives before randomization found that their response rates (a secondary endpoint) were similar to those of the overall study population (43% and 49% with naloxegol 12.5 and 25 mg, respectively, vs 29% with placebo in the first trial, and 47% with naloxegol 25 mg vs 31% with placebo in the second). Median times to first post-dose SBM (another secondary endpoint) in the two studies were 6 and 12 hours with naloxegol 25 mg, compared to 36 and 37 hours with placebo.

Table 1. Pharmacology

| | |
|---|---|
| Class | Peripherally-acting mu-opioid receptor antagonist |
| Formulation | 12.5, 25 mg tablets |
| Route | Oral |
| Tmax | <2 h |
| Metabolism | Primarily by CYP3A |
| Elimination | Feces (68%); urine (16%) |
| Half-life | 6-11 h |

## Adverse Effects

The adverse effects of naloxegol are dose-related; the most common have been GI-related, including abdominal pain, diarrhea, nausea, flatulence, and vomiting. Patients who were receiving methadone as their analgesic had a higher rate of GI adverse effects than those receiving other opioids. GI perforation has been reported with use of methylnaltrexone; naloxegol is contraindicated in patients with GI obstruction or at increased risk of recurrent obstruction. Possible opioid withdrawal (defined as ≥3 adverse effects potentially related to opioid withdrawal, such as hyperhidrosis, chills, anxiety, or irritability, occurring on the same day and not all GI-related) occurred in 3% of patients taking naloxegol 25 mg and in 1% of patients taking 12.5 mg, compared to <1% of those taking placebo.

In a 52-week, open-label safety and tolerability study, 804 patients with opioid-induced constipation were randomized to treatment with naloxegol 25 mg or usual care with a laxative regimen. GI adverse effects and headache occurred more frequently with naloxegol than with usual care. Rates were similar to those observed in the 12-week efficacy studies. No drug-related cases of bowel perforation, opioid withdrawal, or major cardiovascular adverse events were reported, and pain scores and mean daily opioid doses were stable throughout the study in patients treated with naloxegol.[7]

## Pregnancy

Naloxegol is classified as category C for use during pregnancy. There are no adequate studies in pregnant women. No adverse effects were observed in pregnant animals given very high doses of the drug. Use



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Table 2. FDA-Approved Drugs for Opioid-Induced Constipation

| Drug | Formulations | Usual Adult Dosage | Response Rate (Active Drug vs Placebo)[a] | Cost[b] |
|---|---|---|---|---|
| **Mu-Opioid Receptor Antagonists** | | | | |
| Naloxegol - Movantik (AstraZeneca) | 12.5, 25 mg tabs | 25 mg PO once daily[c] | 35%-44% vs 29% | $249.60 |
| Methylnaltrexone - Relistor (Salix/Valeant) | 8 mg/0.4 mL single-use syringes, 12 mg/0.6 mL single-use vials, syringes | 12 mg SC once daily[d] | 59% vs 38% | 2161.80 |
| **Chloride Channel Activator** | | | | |
| Lubiprostone - Amitiza (Sucampo/Takeda) | 8, 24 µg caps | 24 µg PO bid[e] | 27% vs 19% | 314.50 |

[a] In pivotal clinical trials with a primary endpoint that consisted of having ≥3 SBMs per week during a 4-week treatment period (methylnaltrexone), that included having ≥3 SBMs per week for at least 9 of 12 treatment weeks (lubiprostone), or that included having ≥3 SBMs per week during a 12-week treatment period (naloxegol), as summarized in the package insert for each drug.

[b] Approximate WAC for 30 days' treatment. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalog or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. September 5, 2015. Reprinted with permission by First Databank, Inc. All rights reserved. ©2015. http://www.fdbhealth.com/policies/drug-pricing-policy.

[c] Patients who cannot tolerate the higher dose can take 12.5 mg once daily. Tablets should be taken in the morning at least 1 h before or 2 h after a meal. Starting dosage for patients with a CrCl <60 mL/min is 12.5 mg once daily.

[d] Dosage for noncancer pain. For patients with advanced illness, the drug should be given every other day at a dose of 8 mg SC for patients weighing 38 to <62 kg, 12 mg SC for those weighing 62-114 kg, or 0.15 mg/kg SC for those weighing <38 kg or >114 kg. In patients with a CrCl <30 mL/min, the dose should be reduced by one-half.

[e] Taken with food and water. The recommended starting dosage is 16 µg bid for patients with moderate hepatic impairment and 8 µg bid for those with severe hepatic impairment.

of naloxegol in women who are pregnant or breastfeeding could precipitate opioid withdrawal in the fetus or infant because of an immature blood-brain barrier.

## Drug Interactions

Coadministration of naloxegol and the strong CYP3A4 inhibitor ketoconazole resulted in a 12.85-fold increase in naloxegol exposure. Such increases could result in opioid withdrawal; concomitant use of naloxegol with any strong CYP3A4 inhibitor is contraindicated. Concurrent administration of the moderate CYP3A4 inhibitor diltiazem increased serum concentrations of naloxegol about 3-fold; the dosage of naloxegol should be reduced to 12.5 mg daily if it must be taken with a moderate CYP3A4 inhibitor. Patients taking naloxegol should avoid consuming grapefruit or grapefruit juice, which inhibit CYP3A4. Strong CYP3A4 inducers such as rifampin can significantly lower serum concentrations of naloxegol and possibly reduce its efficacy.[8]

Taking naloxegol with another opioid antagonist should be avoided because of possible additive effects and an increased risk of opioid withdrawal.

## Dosage and Administration

All maintenance laxatives should be stopped before initiating treatment with naloxegol, but can be restarted after 3 days if symptoms persist. The recommended dosage of naloxegol is 25 mg once daily in the morning at least 1 hour before or 2 hours after a meal; the daily dose can be reduced to 12.5 mg in patients who cannot tolerate the higher dose. The starting dosage for patients with a CrCl <60 mL/min is 12.5 mg once daily. Naloxegol tablets should be swallowed whole and should not be crushed or chewed.

## Conclusion

Naloxegol (Movantik) is the first oral mu-opioid receptor antagonist to be approved for treatment of opioid-induced constipation. It may be more effective than lubiprostone (Amitiza) and is cheaper and more convenient to administer than methylnaltrexone (Relistor), the other drugs approved for this indication (**Table 2**), but no direct comparisons are available. It has not been studied in patients taking opioids for cancer pain. Laxatives and stool softeners should generally be tried first.


### ARTICLE INFORMATION

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