Formulary Review: Movantik®
Generic Name: naloxegol
Manufacturer: AstraZeneca
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Executive Summary

Introduction

Naloxegol is FDA approved opioid antagonist indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain.

Pharmacology

At recommended doses, naloxegol acts as a peripheral mu-opioid receptor antagonist that exerts its effects in the gastrointestinal tract, alleviating the constipating effects of opioids. Naloxegol has limited CNS penetration due to its PEG moiety that reduces passive diffusion and its efflux across the blood-brain barrier as a P-glycoprotein substrate.

Pharmacokinetics

Table 1: Pharmacokinetic profile

Absorption	• Time to peak < 2 hours • High-fat foods increases C_{max} and AUC by 30% and 45%, respectively
Distribution (V_d)	• 968-2140L
Protein Binding	• 4.2%
Metabolism	• Hepatic by CYP3A • No major metabolites • Minor metabolites via N-dealkylation, O-demethylation, oxidation and partial loss of the PEG chain.
Elimination	• 68% feces (16% unchanged) • 16% urine (< 6% unchanged)
Elimination half-life	• 6-11 hours

Clinical Efficacy

Two separate double-blinded, placebo-controlled trials assessed the safety and efficacy of naloxegol in patients with opioid-induced constipation with chronic non-cancer pain. Eligible patients were on opioids for an average of 3.6 years (Study 04) and 3.7 years (Study 05) and reported having less than 3 spontaneous (i.e. not laxative assisted) bowel movements per week. A combined total of 1252 patients were randomized 1:1:1 to receive either placebo, 12.5 mg naloxegol, or 25 mg naloxegol daily for 12 weeks.

The primary endpoint was defined as greater than 3 spontaneous bowel movements per week and an improvement from baseline of at least one more spontaneous bowel movement per week for 9 out of the 12 weeks and for 3 out of the last 4 weeks.

- In the first study (n=652), 29% (63/214) of patients achieved the primary endpoint in the placebo group, 41% (87/213) in the 12.5 mg naloxegol group, and 44% (95/214) in 25 mg naloxegol group. Statistical significance was achieved with both treatment doses, with treatment differences of 11.4% (p = 0.015, 95%CI: 2.4%-20.4%) and 15.0% (p = 0.001, 95%CI: 5.9%-24%) in the 12.5 mg and 25 mg treatment arms respectively.
- In the second study (n=700), 29% (68/232) of patients achieved the primary endpoint in the placebo group, 35% (81/232) in the 12.5 mg naloxegol group, and 40% (92/232) in 25 mg naloxegol group. Statistical significance was achieved with only the 25 mg treatment dose, with a treatment difference of 10.3% (p = 0.021, 95%CI: 1.7%-18.9%).

Secondary endpoints included a subpopulation analysis of patients with an inadequate response to laxatives prior to enrollment, which comprised of > 50% of the study population. Inadequate response was defined as those who took ≥ 1 class of laxative for at least 4 days within the 2 weeks before screening and symptoms were rated as moderate, severe, or very severe per baseline questionnaire. In the subpopulation analysis of patients that had inadequate response to laxatives before enrollment, a higher response rate was observed in the 25 mg naloxegol group compared to placebo (study 04, 48.7% vs. 28.8%, p = 0.002; study 05, 46.8% vs. 31.4%, P = 0.01).

Another secondary endpoint assessed time to the first spontaneous bowel movement. Overall, the median time for the first spontaneous bowel movement was 5.9 hours in Study 04 and 12 hours in Study 05 for patients on the 25 mg dose.

In both studies, patients were not allowed to take any additional laxatives except in instances of when the patient did not have a bowel movement for 72 hours. In these instances, a rescue therapy was permitted, which comprised of no more than three doses of 10-15 mg of bisacodyl, followed by an enema as needed. A greater percentage of patients required ≥ 1 rescue therapy in the placebo groups (72% in Study 04 and 75% in Study 05) compared to the naloxegol 12.5 mg

treatment groups (63.4% in Study 04 and 57.3% in Study 05) and 25 mg treatment groups (54.7% in Study 04 and 54.7% in Study 05).

Adverse Reactions

Common adverse events for the 25 mg and the 12.5 mg treatment groups included abdominal pain (25% vs 12%), diarrhea (9% vs 6%) and nausea (8% vs 7%). Other less common adverse events included flatulence, vomiting, and headache.

Drug Interactions

CYP3A4 inhibitors: CYP3A4 inhibitors increase serum naloxegol concentrations. Concomitant use with strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, grapefruit) is contraindicated and concomitant use with moderate CYP3A4 inhibitors (e.g. diltazem, erythromycin, verapamil) should be avoided if possible. If use with moderate CYP3A4 inhibitor is unavoidable, limit naloxegol dose to 12.5 mg and monitor for adverse reactions.

CYP3A4 inducers: Strong CYP3A4 inducers (e.g. rifampin, carbamazepine, St. John's Wort) significantly decrease naloxegol concentration – avoid concomitant use.

Opioid antagonists: Additive effects may occur with other opioid antagonist, increasing risk for opioid withdrawal symptoms. Avoid concomitant use.

Contraindications

Naloxegol is contraindicated in patients with confirmed, suspected, or at increased risk for gastrointestinal obstruction, including patients with reduced gastrointestinal structural integrity (e.g. peptic ulcer disease, Ogilvie's syndrome, diverticular disease). Patients on a strong CYP3A4 inhibitor should not take naloxegol due to increased risk of opioid withdrawal symptoms.

Warnings/Precautions

Patients with compromised gastrointestinal tract (e.g. peptic ulcer disease, Ogilvie's syndrome, diverticular disease) have an increased risk for gastrointestinal perforations while on peripherally acting opioid antagonists such as naloxegol. If severe abdominal pain is experienced, discontinue use.

Patients may experience opioid withdrawal symptoms, including hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, irritability, and yawning while on naloxegol. Patients with disrupted blood brain barrier may be at higher risk for these symptoms. During clinical trials, patients on methadone experienced more frequent gastrointestinal opioid withdrawal symptoms compared to patients on other opioids.

Pregnancy/Lactation

Pregnancy Category C. Naloxegol was not studied in pregnant women. No effects on embryo-fetal development were observed in animal studies at doses up to 1452 times human AUC (70 mg/kg/day). Risk of fetal opioid withdrawal due to immature blood brain barrier.

Risk of opioid withdrawal in nursing infants. Naloxegol was excreted in rat milk and absorbed by rat pups.

Specific Populations

The safety and efficacy is not known in pediatric patients.

No dosage adjustment is necessary in patients ≥ 65 years of age. Similar safety and efficacy were reported in geriatrics.

The safety and efficacy is not known in patients with severe hepatic impairment (Child-Pugh Class C).

A lower starting dose is recommended for patients with CrCl ≤ 60 mL/min. Patients with renal impairment showed increased serum concentrations and are at increased risk for adverse side effects

Dosage/Administration

Patients on naloxegol should limit the use of laxatives to only when there is no therapeutic response after three days of therapy. Naloxegol should be taken on an empty stomach, 1 hour prior to the first meal of the day or 2 hours after the meal.

The recommended dosing for naloxegol is 25 mg once daily in the morning; the dose may be decreased to 12.5 mg once daily if not tolerated. Patients with impaired renal function (CrCl ≤ 60 mL/min) should start with 12.5 mg once daily and titrate to 25 mg once daily as tolerated.

Look-alike/Sound-alike

None reported by ISMP at this time.

Table 2. Comparison of available agents

	Movantik ® (naloxegol)	Entereg ® (alvimopan)	Relistor ® (methylnaltrexone)	Amitiza® (lubiprostone)
Mechanism	peripheral mu-opioid receptor antagonist, the alleviating constipating effect of opioids	peripheral mu-opioid receptor antagonist, the alleviating constipating effect of opioids	peripheral mu-opioid receptor antagonist, the alleviating constipating effect of opioids	sodium chloride channel (CIC-2) activator in apical intestine, increasing intestinal fluid secretion and intestinal motility
Time to Peak	< 2 hours	Parent drug: 2 hours Active Metabolite: 36 hours	30 min (SubQ)	0.9-1.4 hours
Elimination Half Life	6-11 hours	10-17 hours	8 hours	1 hour
FDA approved indication	Opioid-induced constipation	Management of postoperative ileus	Opioid-induced constipation with non-cancer pain Opioid-induced constipation with advanced illness	Chronic idiopathic constipation Irritable bowel syndrome with constipation Opioid-induced constipation
Dose	25 mg PO daily If CrCl < 60 mL/min, on moderate CYP3A4 inhibitors, or if unable to tolerate 25 mg, reduce dose to 12.5 mg daily	Prior to surgery: 12.5 mg PO 30 minutes to 5 hours prior to surgery, then After surgery: 12 mg PO twice daily beginning the day after surgery for no more than 7 days or until discharged from hospital (maximum of 15 doses)	Opioid induced constipation with non-cancer pain: 12 mg SubQ once daily Opioid-induced constipation with advanced illness: • < 38 kg: 0.15 mg/kg (round to nearest 0.1 mL) • 38 to < 62 kg: 8 mg • 62 to 114 kg: 12 mg • > 114 kg: 0.15 mg/kg (round to nearest 0.1 mL)	Chornic idiopathic constipation: 24 mcg PO twice daily Irritable bowel syndrome with constipation: 8 mcg PO twice daily Opioid-induced constipation: 24 mcg PO twice daily
Cost	$7.88/ 25 mg tablet $7.88/ 12.5 mg tablet	$114.32/ cap	$94.69/ 8 mg vial $94.69/ 12 mg vial	$4.91/ 24 mcg tablet $4.91/ 8 mcg tablet
Daily Cost	$7.88	$228.63	≥ $94.69	$9.82
Formulary status	Non-formulary	Formulary—restricted to small or large bowel resection with primary anastomosis	Formulary—restricted to use in palliative care and oncology setting	Formulary

Recommendation

- Add naloxegol to the formulary but restrict its use to patients with opioid-induced constipation that have failed two or more laxatives.
- Restrict methylnaltrexone to palliative care and oncology patients that are NPO.

References

1. Movantik [package insert]. AstraZeneca Pharmaceuticals LP, Wilmington, DE; January 2015.
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3. Chey WD, Webster L, Sostek M, Lappalainen J, Barker PN, Tack J. Naloxegol for opioid-induced constipation in patients with noncancer pain. *N Engl J Med.* 2014;370(25):2387-2396.