PDL DRUG REVIEW

Proprietary Name: Movantik®
Common Name: naloxegol
PDL Category: Constipation: Chronic, IBS-C, or Opioid Induced

Comparable Products	Preferred Drug List Status
Amitiza	Non-Preferred with Conditions

Summary

Indications and Usage: Treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain. This is a pregnancy category C medication. The safety and efficacy of use in children have not been established.

Dosage Forms: Film-coated tablets: 12.5mg, 25mg

Recommended Dosage: Discontinue all maintenance laxative therapy prior to starting Movantik®. Take 25mg QAM on an empty stomach ≥1 hour prior to the first meal of the day or 2 hours after the meal; reduce to 12.5mg QAM if not able to tolerate. If there is a suboptimal response to Movantik® after 3 days, laxatives can be added as needed. Discontinue Movantik® once opioid pain medication has been discontinued.

Dose adjustments are not required for those with mild renal or mild to moderate hepatic impairment. Use should be avoided in those with severe hepatic impairment, as a dosage in this population has not been determined. A starting dose of 12.5mg QD is recommended in those with CrCl <60ml/minute (i.e moderate, severe, or end-stage renal disease). If the dose is tolerated but symptoms continue, the dose may be increased to 25mg daily in this population, but with caution.

Drug Interactions: Avoid the concomitant use of grapefruit or grapefruit juice with Movantik® treatment. In addition, while the concomitant use with moderate CYP3A4 inhibitors (e.g. diltiazem, erythromycin, and verapamil) should be avoided, reduce the Movantik® dose to 12.5mg QD and monitor for adverse events if concurrent use is unavoidable. The concomitant use with strong CYP3A4 inhibitors is contraindicated.

The concomitant use of Movantik® with strong CYP3A4 inducers (e.g. rifampin, carbamazepine, St. John's Wort) is not recommended. In addition, the concomitant use of Movantik® should be avoided with another opioid antagonist.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Movantik® 25mg) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same or that the active drug was less than placebo.* The most frequently reported adverse events included abdominal pain (14%), diarrhea (4%), nausea (3%), flatulence (3%), vomiting (1%), headache (1%), and hyperhidrosis (>2%).

Possible opioid withdrawal (defined as ≥3 adverse reactions potentially related to opioid withdrawal that occurred on the same day and were not all related to the GI system) occurred in <1% of the placebo group vs 1% of the Movantik® 12.5mg group and 3% of the 25mg group in 2 studies.

Contraindications: In patients with known or suspected gastrointestinal (GI) obstruction and patients at increased risk of recurrent obstruction, due to the potential for GI perforation; Concomitant use of strong CYP3A4 inhibitors (e.g. clarithromycin, itraconazole, ketoconazole); Known hypersensitivity to naloxegol or any component of the compound

Manufacturer: AstraZeneca Pharmaceuticals

Analysis: Naloxegol oxalate, the active ingredient of Movantik®, is an opioid antagonist that binds at the mu-opioid receptor. Naloxegol is a PEGylated derivative of naloxone that when given at recommended doses, is a peripherally-acting mu-opioid receptor antagonist in tissues such as the GI tract. Thus, it decreases the constipating effects of opioids. In addition, due to the PEG moiety, there is reduced permeability across the blood-brain barrier and therefore limited potential for interference with centrally mediated opioid analgesics.

Naloxegol was considered a C-II controlled substance, even though as it is a peripherally acting opioid antagonist there is no risk of abuse or dependency. However, per a 2015 abstract, the DEA removed naloxegol from the schedules of the Controlled Substances Act.[2] The current prescribing information is updated to reflect this.

Two replicate, randomized, double-blind, placebo-controlled 12 week studies were performed to assess the safety and efficacy of Movantik® in adults with opioid-induced constipation and non-cancer related pain. Patients in study 1 (N=652) and study 2 (N=700) received an opioid morphine equivalent daily dose for ≥4 weeks before enrollment into the studies and self-reported OIC. Throughout the studies, only bisacodyl rescue laxative was allowed if they had not had a bowel movement (BM) for 72 hours and a one-time use of an enema if after 3 doses of bisacodyl they still did not have a BM.

The primary endpoint was response, defined as ≥3 spontaneous BM (SBMs) per week and a change from baseline of ≥1 SBM per week for ≥9 out of the 12 study weeks and 3 out of the last 4 weeks. Results from each study are included in the table below, which was adapted from the prescribing information.

Study 1			
	Placebo (N=214)	Movantik® 12.5mg (N=213)	Movantik® 25mg (N=214)
Proportion responding (%)	29% (N=63)	41% (N=87)	44% (N=95)
Treatment difference (Movantik®-placebo)		11.4% (p=0.015)	15% (p=0.001)

Study 2			
	Placebo (N=232)	Movantik 12.5mg (N=232)	Movantik 25mg (N=232)
Proportion responding (%)	29% (N=68)	35% (N=81)	40% (N=92)
Treatment difference (Movantik®-placebo)		5.6% (p=0.202, NS)	10.3% (p=0.021)

(**IME Comments:** The calculated NNTs for study 1 with Movantik 12.5mg and 25mg were 9 and 7, respectively. The NNTs for study 2 were 17 and 10, respectively.)

A secondary endpoint in both studies was response in laxative users with OIC symptoms. In this subgroup, 42% in study 1 and 50% in study 2 reported using laxatives on a daily basis. In study 1, there was a statistically significantly

higher % in this subgroup who responded to Movantik® 12.5mg vs placebo (43% vs 29%; p=0.03) and with Movantik® 25mg vs placebo (49% vs 29%; p=0.002). In study 2, this secondary endpoint was not tested for the 12.5mg dose as the primary endpoint was not statistically significant; however, a statistically higher % in this subgroup responded with Movantik® 25mg vs placebo (47% vs 31%; p=0.01).

Another secondary endpoint was the time to the first post-dose SMB. For study 1, the median times to first post-dose SBM were 6 hours for Movantik® 25mg vs 20 hours for Movantik® 12.5mg and 36 hours for placebo. For study 2, the median times were 12 hours for Movantik® 25mg vs 37 hours for placebo. The time to first post-dose SBM was significantly shorter with Movantik® 25mg vs placebo in study 1 and 2 ($p<0.001$ for both) and with Movantik® 12.5mg in study 1 ($p<0.001$). In the two studies, 61-70% receiving Movantik® 25mg and 58% receiving the 12.5mg dose had a SBM within 24 hours of the first dose. A third secondary endpoint assessed the change from baseline between the treatments for mean number of days per week with ≥1 SBM but no more than 3 SBMs. A significant difference in the number of days per week with 1-3 SBMs per day was seen with Movantik® 25mg vs placebo in study 1 and 2 and with Movantik® 12.5mg vs placebo in study 1 over the 12 weeks.

Place in Therapy: Dietary modifications, such as increased intake of fluids and dietary fiber, may improve bowel functions. Numerous pharmacologic agents are available for laxative therapy if dietary modification alone is not enough. One noted reference source suggested that with refractory cases of opioid-induced constipation, the opioid antagonists may be helpful.[3] Movantik® is an opioid antagonist indicated for OIC with chronic non-cancer pain. It was shown to be effective in those who have taken opioids for ≥4 weeks. A long-term safety study by Webster et al[4] suggested that naloxegol was generally safe and well tolerated for up to 52 weeks.

It is recommended that Movantik® remain non-preferred and require prior authorization to verify diagnosis and prior trials of preferred agents.

PDL Placement:

- ☐ **Preferred**
- ☒ **Non-Preferred with Conditions**
- ☐ **Preferred with Conditions**

References

[1] Movantik [package insert]. Wilmington, DE: AstraZeneca; 2015.

[2] Drug Enforcement Administration, Department of Justice. Schedules of controlled substances: removal of naloxegol from control. Final rule. *Fed Registr*. 2015; 80(15): 3468-70.

[3] UpToDate desktop version. Overview of the treatment of chronic pain. Accessed August 2015.

[4] Webster L, Chey WD, Tack J, et al. Randomized clinical trial: the long-term safety and tolerability of naloxegol in patients with pain and opioid-induced constipation. *Aliment Pharmacol Ther*. 2014; 40(7): 771-9.