Naloxegol Oxalate (MOVANTIK) Tablets
National Drug Monograph
July 2015
VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information

Description/Mechanism of Action	Naloxegol (MOVANTIK, AstraZeneca) is a PEGylated derivative of naloxone. At the recommended dose levels, naloxegol functions as a peripherally acting mu-opioid receptor antagonist (PAMORA) to reduce the constipating effects of opioid therapy and increase spontaneous bowel movements. The PEG moiety of naloxegol promotes P-glycoprotein transport of naloxegol out of the central nervous system, effectively limiting its ability to cross the blood-brain barrier and antagonize mu-opioid receptor mediated analgesia.[1,2]
Indication(s) Under Review in this Document	FDA-approved Indication(s): Treatment of opioid-induced constipation in adult patients with chronic non-cancer pain. Off-label Use(s): None
Dosage Form(s) Under Review	Oral tablets, 12.5 mg and 25 mg
REMS	☐ REMS ☒ No REMS Post-marketing Study Requirements: N/A
Pregnancy Rating	C

Executive Summary

Efficacy	• Naloxegol significantly increased the number of spontaneous bowel movements per week relative to placebo in two of two phase III trials at a dose of 25 mg daily and one of two phase III trials at 12.5 mg daily over a 12-week treatment period.[3,4] • A shorter time to first post-dose spontaneous bowel movement was observed in both trials for naloxegol 25 mg daily ($P<0.001$) and only one trial for 12.5 mg daily ($P<0.001$) relative to placebo.[4] • Pain scores and daily opioid doses did not differ from baseline between treatment and placebo groups in either of the two phase III efficacy and safety trials reviewed.[3] • Efficacy has not been studied beyond a 12-week treatment period, nor have trials involving active comparators been published. [3,4]
Safety	• Abdominal pain, diarrhea, nausea and vomiting are the most common adverse events associated with naloxegol.[3,5] • No life threatening adverse events were reported in the two phase III efficacy and safety trials (KODIAC-04/05) and the one phase III long-term safety trial (KODIAC-08) available to date.[3,5] • No data supporting safe use beyond twelve months is available.[5] • Adjust dosage in renal impairment; use caution in hepatic impairment.[1]
Potential Impact	• Naloxegol may be effective for short-term use in Veterans who have failed non-pharmacologic strategies and multiple therapeutic alternatives (i.e., stimulant ± surfactant and osmotic agents) for promoting spontaneous bowel movements. • Naloxegol has potential advantages over similar products. Other FDA-approved PAMORAs either require subcutaneous injection or have an unacceptable cardiac profile for use in opioid-induced constipation.

Background

Purpose for review

Newly approved drug.

Issues to be determined:

- Short and long-term efficacy and safety of naloxegol relative to alternative therapies.
- Potential advantages and disadvantages of naloxegol.
- Patient factors that influence subgroup response for safety and efficacy.

Other therapeutic options

Formulary Alternatives	Other Considerations
Surfactant Docusate capsule, rectal enema, oral liquid (OTC)	Not FDA approved and has limited efficacy for opioid-induced constipation, dosed 1 to 4 times daily, minimal safety risk, extensive history of use and available OTC, onset of action 1 – 3 days. [6]
Osmotic Agents PEG-3350 powder, oral Lactulose syrup Magnesium citrate liquid (OTC) Magnesium hydroxide susp (OTC)	Not FDA approved for opioid-induced constipation, minimal safety risk, extensive history of use and most available OTC; onset of action 1 – 3 hours PO. [6]
Stimulant Laxatives Bisacodyl EC tablet (OTC) Sennosides tablet (OTC)	Recommended first-line agents for opioid-induced constipation despite paucity of quality studies; given orally once daily(or twice daily for sennosides); most common adverse effect abdominal cramping; extensive history of use and available OTC; onset of action 6 – 12 hours PO, < 2 hours rectally. [6]
Combination Surfactant / Stimulant Docusate / Sennosides tablet (OTC)	Recommended first-line agents for opioid-induced constipation; given orally 2 – 4 times daily; onset of action 6 to 12 hours. [7,8]
Bulk-Forming Laxatives Psyllium powder, oral (OTC) Cellulose, oxidized powder, oral Calcium Polycarbophil tablet	NOT recommended for opioid-induced constipation because of potential for bowel obstruction; onset of action 1 – 3 days PO. [6]
Lubricant Mineral oil, heavy 100% (OTC)	NOT recommended for use as a laxative, acute or chronic aspiration may result in lipoid pneumonitis. [9]

Non-formulary Alternative	Other Considerations
PAMORA (for injection) Methylnaltrexone subcutaneous injection	Effective PAMORA indicated for opioid-induced constipation in adults with chronic noncancer pain (dosed once daily) and patients with advanced illness (dosed every other day p.r.n.); abdominal pain common, risk of gastrointestinal perforation and opioid withdrawal; onset of action ~30 minutes. [10]
PAMORA (oral) Alvimopan capsule	PAMORA only indicated to accelerate gastrointestinal recovery following certain surgeries; increased risk of myocardial infarction with long-term use and has a REMS to limit therapy to 15 days; onset of action 4 – 7 hours. [11]
Chloride Channel Activator Lubiprostone capsule	FDA-approved for opioid-induced constipation in patients with chronic noncancer pain, twice daily dosing with food; common adverse effects are nausea, headache and diarrhea; onset of action < 24 hours. [12]
Guanylate Cyclase-C Agonist Linaclotide capsule	Indicated for idiopathic constipation, once daily dosing; most common adverse effect abdominal pain; possible severe diarrhea; onset of action 22 – 24 hours. [13]

Efficacy (FDA-approved Indications)

Literature Search Summary
A literature search was performed on PubMed/Medline (1966 to August 2014), ClinicalTrials.gov and the Cochrane Central Register of Controlled Trials using the search terms naloxegol, Movantik and NKTR-118.The search was limited to studies performed in humans.

References cited in the manufacturer's AMCP dossier and in review articles were searched for relevant trials. All relevant trials published in peer-review journals were included in this monograph. In addition, the FDA Medical Review provided additional and unpublished information. The UK's NICE Web site was also searched (www.nice.org). A technology appraisal for naloxegol is due to be published in July 2015. The European Medicines Agency's Committee for Medicine Products for Human Use (CHMP) Summary of Opinion on naloxegol was also consulted.[14]

Review of Efficacy

The literature search found no active comparator trials involving naloxegol. Two identical multicenter, randomized, double-blind, parallel-group phase III trials evaluated naloxegol relative to placebo. These AstraZeneca-sponsored trials are known as KODIAC-04 and KODIAC-05. Both trials were reported as a single publication. Patients eligible for inclusion in KODIAC-04 and KODIAC-05 were 18 – 84 years old and receiving oral opioids for non-cancer pain at a morphine equivalent dose of 30 – 1000 mg/day for at least four weeks. Patient eligibility was confirmed during a 2-week screening period. Patients meeting study criteria kept a diary to record symptoms of active opioid-induced constipation for two additional weeks. Constipation was defined as less than three spontaneous bowel movements per week with one or more of the following: hard or lumpy stools, straining, or incomplete evacuation for at least 25% of bowel movements. Major exclusion criteria included uncontrolled pain despite opioid analgesic therapy, cancer within five years of study enrollment, medical conditions associated with diarrhea or constipation, evidence of gastrointestinal obstruction or conditions that increase risk of bowel perforation. The trial protocols included a randomization procedure to ensure at least 50% of each study arm contained patients with an inadequate laxative response which required patients to have utilized one or more laxative classes for a minimum of four days within two weeks before screening and have stool-symptoms rated as moderate or greater on a baseline laxative-response questionnaire. Throughout the confirmation and treatment period laxatives and other bowel treatments were not allowed; however, patients were allowed bisacodyl rescue if a bowel movement had not occurred within 72 hours.[3]

The study groups' baseline characteristics and efficacy results are reported in Table 1.

Table 1 – KODIAC Trials: Baseline Characteristics and Efficacy Results

Population Characteristic || Outcome Measure	Placebo Control	Naloxegol 12.5 mg daily	Naloxegol 25 mg daily
KODIAC-04 Trial [3]			
N	214	213	214
Age, yr	52.9 ± 10.0	51.9 ± 10.4	52.2 ± 10.3
Duration of opioid use, months	39.5 ± 39.4	44.4 ± 47.3	44.5 ± 47.8
Opioid dose, mg/day	135.6 ± 145.8	139.7 ± 167.4	143.2 ± 150.1
Spontaneous bowel movements per week	1.4 ± 0.89	1.4 ± 0.85	1.3 ± 1.11
Inadequate response to laxatives,[†] %	55.1	54.0	54.7
Response[§] rate over 12-week treatment, % (PEM)	29.4	40.8*	44.4*
Difference vs. placebo (95% CI), pp	--	11.4 (2.4–20.4)	15.0 (5.9–24.0)
NNT (95% CI)		9 (5–42)	7 (4–17)
Response[§] rate over 12-week treatment in patients with inadequate response to laxatives, %	28.8	42.6*	48.7*
Difference vs. placebo (95% CI), pp	--	13.8 (1.6–26.0)	19.9 (7.7–32.1)
NNT (95% CI)		7 (4–63)	5 (3–13)
Median time to first spontaneous bowel movement, h	35.8	20.4	5.9
Change from baseline, number of spontaneous bowel movements per week, mean ± SE	2.02 ± 0.18	2.56 ± 0.18	3.02 ± 0.18
Percent who used bisacodyl rescue at least once, %	72.0	63.4	54.7
KODIAC-05 Trial [3]			
N	232	232	232
Age (year)	52.3 ± 11.6	52.0 ± 11.0	51.9 ± 12.1
Duration of opioid use (months)	43.0 ± 51.4	48.5 ± 48.7	40.9 ± 41.6

Opioid dose (mg/day)	119.9 ± 103.8	151.7 ± 153.0	136.4 ± 134.3
Spontaneous bowel movements per week	1.5 ± 0.95	1.6 ± 1.05	1.3 ± 0.85
Inadequate response to laxatives,[†] %	52.2	53.9	53.4
Response[§] rate over 12-week treatment, % (PEM)	29.3	34.9	39.7*
Difference vs. placebo (95% CI), pp	--	5.6 (-2.9–14.1)	10.3 (1.7–18.9)
NNT (95% CI)		18 (7–34)	10 (5–59)
Response[§] rate over 12-week treatment in patients with inadequate response[¶] to laxatives, %	31.4	42.4	46.8*
Difference vs. placebo (95% CI), pp	--	11.0 (-1.0–23.0)	15.4 (3.3–27.4)
NNT (95% CI)		10 (4–100)	7 (4–30)
Time to first spontaneous bowel movement, h	37.2	19.3	12.0
Change from baseline, number of spontaneous bowel movements per week, mean ± SE	2.10 ± 0.18	2.62 ± 0.18	3.14 ± 0.19
Percent who used bisacodyl rescue at least once, %	70.7	57.3	57.3

PEM, Primary efficacy measure; pp, Percentage points
* Indicates P<0.05 for comparison with placebo.
[†] Prior laxatives were mainly stimulants and stool softeners
[§]Response was defined as three or more spontaneous bowel movements (SBM) per week and increase of one or more SBM over baseline for at least 9 of 12 weeks and at least 3 of the final 4 treatment weeks (without the use of bisacodyl rescue or enema in the previous 24 hours).
[¶]Inadequate response to laxatives was defined as those who took one or more classes of laxatives for a minimum of 4 days within 2 weeks before screening and whose symptoms were reported as moderate or greater in at least one of the four stool-symptom domains on the baseline laxative-response questionnaire.

- There is moderate quality evidence that naloxegol has a small effect size relative to placebo in patients with opioid-induced constipation with opioid daily doses of 30-1000 mg per day over a treatment period of 12-week.[3,4]
- In both pivotal trials the 25-mg dose showed a statistically significant benefit for the primary endpoints of 1) response over 12-weeks and 2) response in inadequate laxative responders over 12-weeks. The 12.5 mg dose was statistically significant for both of the primary endpoints only in the KODIAC-04 trial.[3]
- There is moderate quality evidence that naloxegol is efficacious in patients who have a history of inadequate response to laxatives.[3]
- Both naloxegol treatment groups (12.5 and 25 mg) in KODIAC-04 and KODIAC-05 had bisacodyl rescue utilization at least once over the 12-week treatment in at least 50% of trial participants.[3] No subgroup analysis (pre-hoc or post-hoc) were reported for the bisacodyl rescue utilizers.
- There are no published studies that compare the efficacy of naloxegol with usual care or other treatment modalities. Nor are any Cochrane systematic reviews or meta-analyses for naloxegol available.
- AstraZeneca, the manufacture of naloxegol, sponsored and may have had influence in the decision to publish the KODIAC trials.

Potential Off-Label Use

- Post-operative ileus, following partial bowel resection surgery.
- Opioid-induced constipation in patients with active malignancies or metastatic disease.

Safety (For more detailed information refer to the Prescribing Information)

	Comments
Boxed Warning	• None
Contraindications	• Known or suspected gastrointestinal obstruction and an increased risk of recurrent obstruction due to the potential for gastrointestinal perforation. • Concomitant use with strong CYP3A4 inhibitors (e.g., clarithromycin, ketoconazole) because these medications can significantly increase exposure to naloxegol and may precipitate opioid withdrawal symptoms such as hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, irritability, and yawning. • Known serious or severe hypersensitivity reaction to naloxegol or any of its excipients.
Warnings/Precautions	• **Gastrointestinal Perforation:** Gastrointestinal perforation has been reported with other peripherally acting mu-opioid receptor antagonists. Use caution when considering use of naloxegol in patients with localized or diffuse reduction in structural integrity in the wall of the gastrointestinal tract (e.g., peptic ulcer disease, Ogilvie's syndrome, diverticular disease, gastrointestinal malignancies or peritoneal metastases). Monitor for severe, persistent or worsening abdominal pain; discontinue naloxegol in patients if this develops. • **Opioid Withdrawal:** Symptoms consistent with opioid withdrawal (e.g., hyperhidrosis,

chills, diarrhea, abdominal pain, anxiety, irritability and yawning) have occurred in patients treated with naloxegol. Patients with disruptions to the blood-brain barrier may be at higher risk for opioid withdrawal symptoms. Monitor for symptoms of opioid withdrawal in patients as risk.

Safety Considerations

- There is moderate-quality evidence that naloxegol is relatively safe and well tolerated over a 12-month period.[5]
- Most adverse effects are mild to moderate in intensity.[3,4,5]
- There is insufficient evidence for naloxegol's long-term safety (>1 year); the KODIAC-08 trial examined the safety of naloxegol relative to usual care for 52-weeks (mean exposure 268 days).[5]
- The KODIAC trial series did not have adequate power to detect rare events, such as gastrointestinal perforations; therefore the possibility of this event cannot be excluded.[5]
- No myocardial infarctions were attributed to naloxegol in the KODIAC trial series. However, alvimopan, an oral agent in the same class as naloxegol, has been associated with an increased risk of myocardial infarction with long-term use. With little clinical experience and minimal phase IV post-marketing surveillance for naloxegol, the possibility of a class effect cannot be disregarded.[15]
- Patients with severe renal impairment (eGFR <30mL/min/1.73m^2) were observed to have twice the drug exposure (area under the curve) and a 15% greater C_{MAX} than patients with normal function.[16]

Adverse Reactions

Common Adverse Effects

Adverse Effect (AE)	Frequency (%) with placebo	Frequency (%) with naloxegol 12.5 mg	Frequency (%) with naloxegol 25 mg
Serious AE*	5.2	5.2 – 6.1	3.3 – 3.4
Any AE	46.9 – 58.9	49.3 – 59.6	61.2 – 69.0
Abdominal pain	3.3 – 7.8	8.5 – 10.9	12.6 – 19.0
Diarrhea	4.2 – 4.3	3.3 – 7.8	9.3 – 9.1
Nausea	4.7 – 4.3	6.1 – 7.1	7.5 – 8.6
Vomiting	2.6 – 3.3	1.4 – 3.0	2.8 – 6.0
Headache	1.9 – 3.5	2.4 – 5.2	3.7 – 5.2
Flatulence	1.9 – 3.0	1.7 – 4.3	5.6 – 6.0

*Serious AE defined as an event resulting in death, immediately life-threatening, required or prolonged hospitalization or substantial inhibition of ability to conduct normal life functions. Data reported from: KODIAC-04/05

Deaths/Serious Adverse Events

- No deaths were attributed to naloxegol in KODIAC-04, KODIAC-05 or KODIAC-08.
- Similar rates of serious adverse events were observed in all study groups in KODIAC trials.
- No bowel perforations were reported in any of the KODIAC trials.

Discontinuations Due to Adverse Events

	Frequency (%) with placebo	Frequency (%) with naloxegol 12.5 mg	Frequency (%) with naloxegol 25 mg
Adverse events leading to discontinuation	5.2 – 5.6	4.3 – 5.2	10.3
Diarrhea			2.8 – 3.4
Abdominal pain			1.9 – 3.9
Nausea			1.7
Vomiting			1.7

*Reported AEs leading to discontinuation occurred in at least three study participants (KODIAC-04/05). Discontinuation event breakdown only reported for naloxegol 25 mg group.

Drug Interactions

Drug-Drug Interactions

- Strong CYP3A4 inhibitors — Contraindicated, avoid concurrent use

• Moderate CYP3A4 inhibitors	Avoid concurrent use if possible, if necessary reduce dose to 12.5 mg daily
Drug-Food Interactions	Grapefruit
Drug-Lab Interactions	None found
Drug-Disease Interactions	Use with caution in patients with conditions that have the potential to increase permeability of the blood-brain-barrier. If used in this population, monitor for signs and symptoms of opioid withdrawal.

Risk Evaluation

As of December 5, 2014

Sentinel event advisories	None found	
Look-alike / sound-alike error potential	**NME Drug Name**	**Drugs with LASA Risk**
	Movantik ™	Myfortic ™, Myrbetriq ™
	naloxegol	naloxone, naproxen, naltrexone
	NME = New Molecular Entity	

Other Considerations

Efficacy Comparison to Active Control	All efficacy data published to date is relative to placebo.
Quality of Life Data	There is no published data evaluating naloxegol's effect on quality of life.

Dosing and Administration

- The recommended Movantik (naloxegol) dosage is 25 mg once daily in the morning.
- If patients are not able to tolerate Movantik (naloxegol), reduce the dosage to 12.5 mg once daily.
- Refer to the Prescribing Information for full, up-to-date dosing and administration information.

Special Populations (Adults)

Elderly	Naloxegol exposure was noted to be higher in elderly Japanese subjects compared to young subjects. However, overall no differences in the safety and efficacy of naloxegol were observed in clinical trials. Eleven percent of subjects studied were 65 and older and two percent 75 and older.
Pregnancy	Pregnancy Category C – Use in pregnancy not sufficiently studied. Potential risk to fetus of opioid withdrawal due to underdeveloped blood-brain-barrier. Animal studies did not reveal effect on embryo-fetal development.
Lactation	Infant risk cannot be ruled out. No safety data found.
Renal Impairment	An initial dose of 12.5 mg daily is recommended in patients with a creatinine clearance <60mL/min. If a 12.5 mg daily dose is tolerated and opioid-induced constipation does not resolve, then 25 mg daily may be trialed with continued monitoring for adverse effects.
Hepatic Impairment	Severe hepatic impairment (Child-Pugh Class C): Avoid use; pharmacokinetics not evaluated.
Pharmacogenetics/genomics	No data found

Projected Place in Therapy

- Based on the review of the available moderate-quality evidence, naloxegol has a small effect on constipation in patients with the following characteristics:[17]
    - Opioid-induced constipation for at least four weeks in patients with chronic non-cancer pain
    - Laxative refractory opioid-induced constipation in patients that have failed two or more laxative classes.

- The evidence supports the use of naloxegol in patients with non-cancer opioid-induced constipation who have experienced constipation for at least four weeks and/or have trialed other classes of laxatives without adequate response. Treatment benefits include increased frequency of bowel movements, increased number of bowel movements per week, onset of action in 6 – 12 hours following administration, reduction of straining and improvement in stool consistency.[3]
- Many treatment alternatives exist for opioid-induced constipation such as stimulant laxatives with or without stool softeners or osmotic laxatives.[6,9] Efficacy of naloxegol compared to these treatment modalities has not been studied. The risk of significant adverse events or death from naloxegol is similar to usual care with other classes of laxatives. However, naloxegol treated patients did experience minor adverse effects (e.g., abdominal pain, diarrhea, nausea, flatulence) at a higher rate than patients treated with usual care.[5]
- Potential advantages:
    - Naloxegol is the second orally administered laxative approved for use in opioid-induced constipation.
    - Naloxegol has not been shown to increase risk of bowel perforation or cardiac events.[3,4,15]
- It may be reasonable to consider naloxegol in patients with non-cancer pain who are experiencing opioid-induced constipation and/or are refractory to traditional laxatives. Patients should be limited to a treatment course of 12-weeks or less due to lack of evidence supporting efficacy beyond this time period.

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