

January 21, 2016

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Helena, MT 59602
US

Dear Mr. Campana:

Your MOVANTIK representative has forwarded your request for information regarding MOVANTIK™ (naloxegol) tablets. The following information is being provided, as a professional courtesy, in response to your request:

MOVANTIK-2-page CES

These materials may include information that is not found in the currently approved prescribing information for MOVANTIK™ (naloxegol) tablets. The enclosed information is intended to provide pertinent data in response to your request and should in no way be construed as a recommendation for the use of this product in any manner other than as approved by the Food and Drug Administration and as described in the prescribing information for MOVANTIK™ (naloxegol) tablets. Prescription drugs used in a manner other than their approved indication may not be eligible for reimbursement by any third-party payors, including Medicaid, Medicare, or similar federal or state programs. Prescribing information for MOVANTIK™ (naloxegol) tablets may be obtained from http://www.astrazeneca-us.com/cgi-bin/az_pi.cgi?product=movantik&country=us&popup=no or by calling the Information Center at AstraZeneca at 1-800-236-9933.

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Adverse Event Reporting

In order to monitor the safety of MOVANTIK™ (naloxegol) tablets, we encourage clinicians to report suspected adverse events to AstraZeneca at 1-800-236-9933.

Tel 877 893 1510
Fax 302 885 1400
www.astrazeneca-us.com

Medical Resources FOC/CE1 706, 1800 Concord Pike, PO Box 15437, Wilmington, DE 19850-5437



Thank you for your interest in MOVANTIK™ (naloxegol) tablets. If we may be of further assistance to you, please contact AstraZeneca at 1-877-893-1510.

Sincerely,

Diane Quinn, PharmD.

Senior Medical Information Manager

INQ 00889119

MOVANTIK™ (naloxegol) Tablets
Clinical Executive Summary (last updated: 8-25-15)
AstraZeneca, Wilmington, DE

Some information contained in this response may not be included in the approved MOVANTIK Prescribing Information (PI) and is not intended to offer recommendations for administering this product in a manner inconsistent with its approved labeling. Please consult the complete MOVANTIK PI, which may be obtained from www.astrazeneca-us.com.

Overview

Opioids play an important role in chronic pain relief by binding to mu-receptors in the central nervous system (CNS), but they also bind to mu-receptors in the gastrointestinal (GI) tract, which may result in opioid-induced constipation (OIC).^{1,2} In fact, OIC is one of the most common adverse events seen with opioids. OIC may be a burden to the patient and the health care system. It can limit activities of daily living, decrease productivity, reduce overall health-related quality of life, complicate the management of pain, and potentially increase health care resource utilization and costs.^{1,3,4}

MOVANTIK is a once-daily oral antagonist of opioid binding at the mu-opioid receptor. When administered at recommended doses, MOVANTIK acts as a peripherally acting mu-opioid receptor antagonist (PAMORA) in tissues such as the GI tract, with negligible interference with centrally mediated opioid analgesia.⁵ MOVANTIK has demonstrated efficacy for the treatment of OIC in adult patients with chronic non-cancer pain, including patients who had previously not responded to laxatives, in 2 Phase III pivotal safety and efficacy trials.

Distinguishing Characteristics^{5,6}

- **Targeted Mechanism of Action:** When administered at the recommended dose levels, MOVANTIK functions as a PAMORA in tissues such as the GI tract, thereby decreasing the constipating effects of opioids. MOVANTIK is a PEGylated derivative of naloxone and is a substrate for the P-glycoprotein transporter (P-gp). The presence of the PEG moiety in naloxegol reduces its passive permeability as compared with naloxone. Because of the reduced permeability and increased efflux of naloxegol across the blood-brain barrier, related to P-gp substrate properties, the CNS penetration of naloxegol is expected to be negligible at the recommended dose levels, limiting the potential for interference with centrally mediated opioid analgesia.
- **Once-Daily Oral Dosing:** MOVANTIK provides a once-daily, single oral tablet for the treatment of OIC in adult patients with chronic non-cancer pain.
- **Efficacy and Long-Term Safety Data:** Through the KODIAC clinical trial program, 1497 patients have been exposed to MOVANTIK, including 537 patients for longer than 6 months, and 320 patients for 12 months.
 - In the 2 pivotal safety and efficacy trials (KODIAC 4 and KODIAC 5), MOVANTIK 25 mg resulted in a significantly higher rate of response in patients receiving opioids for chronic noncancer pain with OIC, including those with an inadequate response to laxatives, when compared to placebo.
 - In a 12-week safety extension trial (KODIAC 7) and a 52-week safety and tolerability study (KODIAC 8), the rate and pattern of AEs observed were generally comparable to that seen in pivotal safety and efficacy trials (Table II).

Indication(s) & Dosing⁵

- MOVANTIK is indicated for the treatment of OIC in adult patients with chronic non-cancer pain.
- Discontinue all maintenance laxative therapy prior to initiation of MOVANTIK. Laxative(s) can be used as needed if there is a suboptimal response to MOVANTIK after 3 days.
- Alteration in analgesic dosing regimen prior to initiating MOVANTIK is not required; MOVANTIK should be discontinued if treatment with the opioid medication is discontinued.
- MOVANTIK is administered as a once-daily oral tablet. The recommended dose is 25 mg once daily in the morning. If patients are not able to tolerate MOVANTIK, reduce the dosage to 12.5 mg once daily.
 - The dose for patients receiving moderate cytochrome P450 3A4 (CYP3A4) inhibitors (if use is unavoidable and adverse reactions are monitored) and in patients with creatinine clearance lower than 60 mL/min is 12.5 mg once daily.
 - Concomitant use with strong CYP3A4 inducers is not recommended.
- MOVANTIK should be swallowed whole, and not crushed or chewed, and should be taken on an empty stomach at least 1 hour prior to the first meal of the day or 2 hours after the meal.
- Avoid consumption of grapefruit or grapefruit juice during treatment with MOVANTIK.
- MOVANTIK is contraindicated in patients with known or suspected GI obstruction and in patients at increased risk of recurrent obstruction, in patients receiving strong CYP3A4 inhibitors, and in patients who have had a known serious or severe hypersensitivity reaction to MOVANTIK or any of its excipients.

Clinical Data^{5,6}

The efficacy and safety of MOVANTIK have been confirmed through the KODIAC clinical trial program, which consisted of Phase III trials (2 pivotal efficacy and safety trials, a safety extension trial, and a long-term safety and tolerability trial) of naloxegol for the treatment of OIC in patients with chronic noncancer pain.

In KODIAC 4 and KODIAC 5, 2 identically designed randomized, double-blind, placebo-controlled, Phase III trials evaluating the safety and efficacy of naloxegol for OIC in adult patients with non-cancer pain, the primary efficacy outcome was response over Weeks 1-12. Response was defined as 3 or more spontaneous bowel movements (SBM) per week and an increase of 1 or more SBMs over baseline per week for at least 9 out of the 12 study weeks and at least 3 out of the last 4 weeks. MOVANTIK 25 mg resulted in a statistically significant higher response rate compared with placebo in both KODIAC 4 and 5.

MOVANTIK 12.5 mg was associated with a statistically significant higher response rate compared with placebo in KODIAC 4, but not in KODIAC 5. As such, significance cannot be claimed for any of the key secondary endpoints for the 12.5-mg dose in KODIAC 5. A summary of the results of the primary endpoint and a key secondary efficacy endpoint, response in the subgroup of patients with inadequate response to laxatives before enrollment, from the KODIAC 4 and 5 trials is provided in the following table.

TABLE I: Summary of Response Rate Results From KODIAC 4 and 5.^{3,4}

Endpoint	Trial	MOVANTIK 25 mg	MOVANTIK 12.5 mg	Placebo
Primary Efficacy Endpoint				
Response Rate Over Weeks 1-12 (ITT Population)				
	KODIAC 4	N=214 44.4% (p=0.001)	N=213 40.8% (p=0.02)	N=214 29.4%
	KODIAC 5	N=232 39.7% (p=0.02)	N=232 34.9% (NS)	N=232 29.3%
Key Secondary Efficacy Endpoint				
Response Rate Over Weeks 1-12 (Subgroup of Patients With Inadequate Response to Laxatives Before Enrollment)^a				
	KODIAC 4	N=117 48.7% (p=0.002)	N=115 42.6% (p=0.03)	N=118 28.8%
	KODIAC 5	N=124 46.8% (p=0.01)	N=125 42.4% (NS) ^b	N=121 31.4%

ITT = intention-to-treat; NS = not significant. ^aThis was a subgroup of patients who reported, prior to enrollment, taking medication from ≥ 1 laxative classes for a minimum of 4 days within 2 weeks before screening and whose symptoms were rated as moderate, severe, or very severe in at least 1 of the 4 stool-symptom domains on the baseline laxative-response questionnaire; ^bIn KODIAC 5, because the primary endpoint did not differ significantly between the 12.5-mg group and the placebo group, significance could not be claimed for any of the key secondary endpoints.

Additional key secondary endpoints included the time to first postdose SBM and the mean number of days/week with 1-3 SBMs over Weeks 1-12. The time to first postdose SBM was significantly shorter for MOVANTIK 25 mg versus placebo in both KODIAC 4 and KODIAC 5 and with MOVANTIK 12.5 mg versus placebo in KODIAC 4 (p<0.001 for all). In KODIAC 4 and KODIAC 5, the median time to first postdose SBM was 5.9 and 12 hours in the MOVANTIK 25 mg groups and 35.8 and 37.2 hours in the placebo group, respectively. Treatment with MOVANTIK 12.5 mg and 25 mg in KODIAC 4 and MOVANTIK 25 mg in KODIAC 5 was associated with a statistically significant increase in the mean number of days/week with 1 or more SBMs over Weeks 1-12 (p<0.001 for all); this effect remained consistent over the 12-week treatment period.

Safety⁵

Adverse reactions that occurred in 3% or more of patients receiving MOVANTIK 12.5 mg or 25 mg and at an incidence greater than placebo are provided in the following table. Safety data for patients in a 12-week safety extension study (n=302; KODIAC 7) and in a Phase III, 52-week, multicenter, open-label, randomized safety and tolerability study (n=844; KODIAC 8) are similar to those listed in the following table.

TABLE II: Adverse Reactions^a in Patients With Opioid-Induced Constipation and Noncancer Pain (KODIAC 4 and 5, Pooled Data).³

Adverse Reactions, %	MOVANTIK 25 mg (n=446)	MOVANTIK 12.5 mg (n=441)	Placebo (n=444)
Abdominal pain	21	12	7
Diarrhea	9	6	5
Nausea	8	7	5
Flatulence	6	3	3
Vomiting	5	3	4
Headache	4	4	3
Hyperhidrosis	3	<1	<1

^aAdverse reactions occurring in $\geq 3\%$ of patients receiving MOVANTIK 12.5 mg or 25 mg and at an incidence greater than placebo.

- Cases of GI perforation have been reported with the use of another peripherally acting opioid antagonist in patients with conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the GI tract. Monitor for the development of severe, persistent, or worsening abdominal pain; discontinue MOVANTIK in patients who develop this symptom.
- Symptoms consistent with opioid withdrawal—including hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, irritability, and yawning—occurred in patients treated with MOVANTIK. Patients receiving methadone in the clinical trials were observed to have a higher frequency of GI adverse reactions that may have been related to opioid withdrawal than patients receiving other opioids. Patients with disruptions to the blood-brain barrier may be at increased risk for opioid withdrawal or reduced analgesia. Monitor for symptoms of opioid withdrawal when using MOVANTIK in such patients.
- Additional safety and drug interaction information can be found in the MOVANTIK Prescribing Information.

References:

1. Brock C, Olesen SS, Olesen AE, et al. Opioid-induced bowel dysfunction: pathophysiology and management. *Drugs*. 2012;72:1847-1865.
2. Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. *Pain Physician*. 2008;11(suppl 2):S105-S120.
3. Panchal SJ, Muller-Schwefe P, Wurzelmann JI. Opioid-induced bowel dysfunction: prevalence, pathophysiology and burden. *Int J Clin Pract*. 2007;61:1181-1187.
4. Bell TJ, Panchal SJ, Miaskowski C, et al. The prevalence, severity, and impact of opioid-induced bowel dysfunction: results of a US and European Patient Survey (PROBE 1). *Pain Med*. 2009;10:35-42.
5. MOVANTIK Prescribing Information.
6. Chey WD, Webster L, Sostek M, et al. Naloxegol for opioid-induced constipation in patients with noncancer pain. *N Engl J Med*. 2014;370:2387-2396.