MOVANTIK® (naloxegol) tablets, for oral use

**INDICATIONS AND USAGE**

MOVANTIK® is indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (e.g., weekly) opioid dosage escalation (1)

**CONTRAINDICATIONS**

Known serious or severe hypersensitivity reaction to MOVANTIK or any of its excipients (4)

**WARNINGS AND PRECAUTIONS**

- Opioid withdrawal: Consider the overall risk benefit in patients with disruptions to the blood-brain barrier. Monitor for symptoms of opioid withdrawal (5.1)
- Severe abdominal pain and/or diarrhea: Monitor for the development of symptoms after initiating treatment with MOVANTIK and discontinue if severe symptoms develop. Consider restarting MOVANTIK at 12.5 mg once daily if appropriate (5.2)
- Gastrointestinal perforation: Consider the overall risk benefit in patients with known or suspected lesions of the GI tract. Monitor for severe, persistent or worsening abdominal pain; discontinue if development of symptoms (5.3)

**ADVERSE REACTIONS**

The most common adverse reactions in clinical trials (≥ 3%) are: abdominal pain, diarrhea, nausea, flatulence, vomiting, and headache (6.1)

**DRUG INTERACTIONS**

- Concomitant use with strong CYP3A4 inhibitors (e.g., clarithromycin, ketoconazole) (4, 7.1)
- Known serious or severe hypersensitivity reaction to MOVANTIK or any of its excipients (4)

**DOSE FORMS AND STRENGTHS**

- Tablets: 12.5 mg and 25 mg (3)

**CONTRAINDICATIONS**

- Known serious or severe hypersensitivity reaction to MOVANTIK or any of its excipients (4)

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**8 USE IN SPECIFIC POPULATIONS**

- Pregnancy: May precipitate opioid withdrawal in pregnant women and the fetus (8.1)
- Lactation: Breastfeeding not recommended (8.2)
- Hepatic Impairment: Avoid in severe impairment (8.7)

**DESCRIPTION**

**CLINICAL PHARMACOLOGY**

- Mechanism of Action
- Pharmacodynamics
- Pharmacokinetics

**NONCLINICAL TOXICOLOGY**

- Carcinogenesis, Mutagenesis, Impairment of Fertility

**HOW SUPPLIED/STORAGE AND HANDLING**

**PATIENT COUNSELING INFORMATION**

**MEDICATION GUIDE**

- Revised: 02/2018

**FULL PRESCRIBING INFORMATION**

**1 INDICATIONS AND USAGE**

MOVANTIK® is indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (e.g., weekly) opioid dosage escalation.

**2 DOSAGE AND ADMINISTRATION**

- 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 three days.
- Alteration in analgesic dosing regimen prior to starting MOVANTIK is not required.
- Patients receiving opioids for less than 4 weeks may be less responsive to MOVANTIK.
- Take MOVANTIK on an empty stomach at least 1 hour prior to the first meal of the day or 2 hours after the meal.
- For patients who are unable to swallow the MOVANTIK tablet whole, the tablet can be crushed to a powder, mixed with 4 ounces (120 mL) of water and drunk immediately. The glass should be refilled with 4 ounces (120 mL) of water, stirred and the contents drunk.
- Concomitant use with strong CYP3A4 inhibitors (e.g., clarithromycin, ketoconazole) (4, 7.1)
- Known serious or severe hypersensitivity reaction to MOVANTIK or any of its excipients (4)

**3 DOSAGE FORMS AND STRENGTHS**

- Tablets: 12.5 mg and 25 mg (3)

**4 CONTRAINDICATIONS**

- Known serious or severe hypersensitivity reaction to MOVANTIK or any of its excipients (4)

**5 WARNINGS AND PRECAUTIONS**

- Opioid withdrawal: Consider the overall risk benefit in patients with disruptions to the blood-brain barrier. Monitor for symptoms of opioid withdrawal (5.1)
- Severe abdominal pain and/or diarrhea: Monitor for the development of symptoms after initiating treatment with MOVANTIK and discontinue if severe symptoms develop. Consider restarting MOVANTIK at 12.5 mg once daily if appropriate (5.2)
- Gastrointestinal perforation: Consider the overall risk benefit in patients with known or suspected lesions of the GI tract. Monitor for severe, persistent or worsening abdominal pain; discontinue if development of symptoms (5.3)

**6 ADVERSE REACTIONS**

The most common adverse reactions in clinical trials (≥ 3%) are: abdominal pain, diarrhea, nausea, flatulence, vomiting, and headache (6.1)

**7 DRUG INTERACTIONS**

- Concomitant use with strong CYP3A4 inhibitors (e.g., clarithromycin, ketoconazole) (4, 7.1)
- Known serious or severe hypersensitivity reaction to MOVANTIK or any of its excipients (4)

**8 USE IN SPECIFIC POPULATIONS**

- Pregnancy: May precipitate opioid withdrawal in pregnant women and the fetus (8.1)
- Lactation: Breastfeeding not recommended (8.2)
- Hepatic Impairment: Avoid in severe impairment (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

**DESCRIPTION**

**CLINICAL PHARMACOLOGY**

- Mechanism of Action
- Pharmacodynamics
- Pharmacokinetics

**NONCLINICAL TOXICOLOGY**

- Carcinogenesis, Mutagenesis, Impairment of Fertility

**HOW SUPPLIED/STORAGE AND HANDLING**

**PATIENT COUNSELING INFORMATION**

**MEDICATION GUIDE**

- Revised: 02/2018
2.3 Dosage in Adult Patients with Renal Impairment

The starting dosage for patients with creatinine clearance (CrCl) < 60 mL/min (i.e., patients with moderate, severe or end-stage renal impairment) is 12.5 mg once daily. If this dosage is well tolerated but OIC symptoms continue, the dosage may be increased to 25 mg once daily taking into consideration the potential for markedly increased exposures in some patients with renal impairment and the increased risk of adverse reactions with higher exposures [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].

2.4 Dosage Recommendations due to Drug Interactions

Avoid concomitant use of MOVANTIK with moderate CYP3A4 inhibitor drugs (e.g., diltiazem, erythromycin, verapamil). If concurrent use is unavoidable, reduce the MOVANTIK dosage to 12.5 mg once daily and monitor for adverse reactions [see Drug Interactions (7.1) and Clinical Pharmacology (12.3)].

3 DOSAGE FORMS AND STRENGTHS

MOVANTIK® (naloxegol) tablets is available in two strengths:

- Tablets: 12.5 mg supplied as mauve, oval, biconvex, film-coated, intagliated with “nGL” on one side and “12.5” on the other side.
- Tablets: 25 mg supplied as mauve, oval, biconvex, film-coated, intagliated with “nGL” on one side and “25” on the other side.

4 CONTRAINDICATIONS

MOVANTIK is contraindicated in:

- Patients with known or suspected gastrointestinal obstruction and patients at increased risk of recurrent obstruction, due to the potential for gastrointestinal perforation [see Warnings and Precautions (5.1)].
- Patients concomitantly using strong CYP3A4 Inhibitors (e.g., clarithromycin, ketoconazole) because these medications can significantly increase exposure to naloxegol which may precipitate opioid withdrawal symptoms such as hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, irritability, and yawning [see Drug Interactions (7.1) and Clinical Pharmacology (12.3)].
- Patients who have had a known serious or severe hypersensitivity reaction to MOVANTIK or any of its excipients.

5 WARNINGS AND PRECAUTIONS

5.1 Opioid Withdrawal

Clusters of symptoms consistent with opioid withdrawal, including hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, irritability, and yawning have occurred in patients treated with MOVANTIK [see Adverse Reactions (6.1)]. In addition, patients receiving methadone as therapy for their pain condition were observed in clinical trials to have a higher frequency of gastrointestinal adverse reactions that may have been related to opioid withdrawal than patients receiving other opioids [see Adverse Reactions (6.1)]. The frequency of gastrointestinal adverse reactions was higher in patients receiving MOVANTIK 12.5 mg (12% [45/377]) compared to patients receiving placebo (3% [14/444]). Symptoms included: abdominal pain, abdominal pain upper, abdominal pain lower, and gastrointestinal pain.

6.2 Severe Abdominal Pain and/or Diarrhea

Reports of severe abdominal pain and/or diarrhea have been reported, some of which resulted in hospitalization. Most of the cases of severe abdominal pain were reported in patients taking the 25 mg dosage. Symptoms generally occurred within a few days of initiation of MOVANTIK. Monitor patients for the development of abdominal pain and/or diarrhea with MOVANTIK and discontinue therapy if severe symptoms occur. Consider restarting MOVANTIK at 12.5 mg once daily, if appropriate.

5.3 Gastrointestinal Perforation

Cases of gastrointestinal perforation have been reported with use of another peripherally acting opioid agonist in patients with conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the gastrointestinal tract (e.g., peptic ulcer disease, Ogilvie’s syndrome, diverticular disease, infiltrative gastrointestinal tract malignancies or peritoneal metastases). Take into account the overall risk-benefit profile when using MOVANTIK in such patients. Monitor for symptoms of opioid withdrawal in such patients.

6 ADVERSE REACTIONS

Serious and important adverse reactions described elsewhere in labeling include:

- Opioid withdrawal [see Warnings and Precautions (5.1)]
- Severe abdominal pain and/or diarrhea [see Warnings and Precautions (5.2)]
- Gastrointestinal perforation [see Warnings and Precautions (5.3)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The data described below reflect exposure to MOVANTIK in 1,487 patients in clinical trials, including 537 patients exposed for greater than six months, and 320 patients exposed for 12 months. The safety data described in Table 1 are derived from two double-blind, placebo-controlled trials (Studies 1 and 2) in patients with OIC and non-cancer related pain. Study 3 (n=302) was a safety extension study that allowed patients from Study 1 to continue the same blinded treatment for an additional 12 weeks. Safety data for patients in Study 3 are similar to those listed in Table 1. Study 4 (n=844) was a Phase 3, 52-week, multi-center, open-label, randomized, parallel group, safety and tolerability study of naloxegol versus usual care treatment for OIC (as determined by the investigator and excluding peripheral opioid antagonists) in patients with non-cancer related pain. The population enrolled in Study 4 was similar to that of the other studies. Eligible patients were randomized in a 2:1 ratio to receive either naloxegol 25 mg once daily or usual care treatment for OIC. The most commonly used laxatives in the usual care group were rectal stimulants (e.g., bisacodyl), oral stimulants (e.g., senna), and oral osmotics (e.g., magnesium, sorbitol). Safety data for patients in Study 4 are similar to those listed in Table 1.

Table 1 lists adverse reactions in pooled Studies 1 and 2 occurring in ≥3% of patients receiving MOVANTIK 12.5 mg or 25 mg and at an incidence greater than placebo.

### Table 1. Adverse Reactions in Patients with OIC and Non-Cancer Pain (Studies 1 and 2)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>MOVANTIK 25 mg (n=446)</th>
<th>MOVANTIK 12.5 mg (n=441)</th>
<th>Placebo (n=444)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Pain†</td>
<td>21%</td>
<td>12%</td>
<td>7%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9%</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Nausea</td>
<td>8%</td>
<td>7%</td>
<td>5%</td>
</tr>
<tr>
<td>Flatulence</td>
<td>6%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5%</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>Headache</td>
<td>4%</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>3%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

† Adverse reactions occurring in ≥3% of patients receiving MOVANTIK 12.5 mg or 25 mg and at an incidence greater than placebo.

Includes: abdominal pain, abdominal pain upper, abdominal pain lower, and gastrointestinal pain.

### 7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on MOVANTIK

Table 2 displays the effects of other drugs on MOVANTIK.

### Table 2. Effects of Other Drugs on MOVANTIK

<table>
<thead>
<tr>
<th>Concomitant Agent</th>
<th>Mechanism of Action</th>
<th>Clinical Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CYP3A4 Inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin)</td>
<td>Increase plasma naloxegol concentrations and may increase the risk of adverse reactions [see Clinical Pharmacology (12.3)].</td>
<td>Use with strong CYP3A4 inhibitors is contraindicated [see Contraindications (4)].</td>
</tr>
<tr>
<td>Moderate CYP3A4 inhibitors (e.g., diltiazem, erythromycin, verapamil)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weak CYP3A4 inhibitors (e.g., quinidine, cimetidine)</td>
<td>Clinically significant increases in naloxegol concentrations are not expected.</td>
<td>No dosages adjustments are necessary.</td>
</tr>
<tr>
<td>Grapefruit or grapefruit juice*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other CYP3A4 inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP3A4 Inducers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strong CYP3A4 inducers (e.g., rifampin, carbamazepine, St. John’s Wort)</td>
<td>Significantly decrease plasma naloxegol concentrations and may decrease the efficacy of MOVANTIK [see Clinical Pharmacology (12.3)].</td>
<td>Use with strong CYP3A4 inducers is contraindicated [see Contraindications (4)].</td>
</tr>
<tr>
<td>Other Drug Interactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other opioid antagonists</td>
<td>Potential for additive effect of opioid receptor antagonism and increased risk of opioid withdrawal.</td>
<td>Avoid use with MOVANTIK and other opioid antagonists.</td>
</tr>
</tbody>
</table>

*The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation dependent. Studies have shown that it can be classified as a “strong CYP3A inhibitor” when a certain preparation was used (e.g., high dose, double strength) or as a “moderate CYP3A inhibitor” when another preparation was used (e.g., low dose, single strength).
MOVANTIK® (naloxegol) tablets, for oral use

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited available data with MOVANTIK use in pregnant women are insufficient to inform a drug associated risk of adverse developmental outcomes. MOVANTIK may precipitate opioid withdrawal in the pregnant women and the fetus (see Clinical Considerations).

In animal development studies, no effects on embryo-fetal development were observed following administration of naloxegol in pregnant rats during the period of organogenesis at doses up to 1452 times the human AUC (area under the plasma concentration-time curve) at the maximum recommended human dose. No effects on embryo-fetal development were observed following administration of naloxegol in pregnant rabbits during the period of organogenesis at doses up to 409 times the human AUC at the maximum recommended human dose.

The estimated background risk of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically-recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Maternal and Fetal/Neonatal adverse reactions

The use of MOVANTIK may be associated with opioid withdrawal in the pregnant woman and the fetus.

Data

Animal Data

Oral administration of up to 750 mg/kg/day naloxegol in rats (1452 times the human AUC at the maximum recommended human dose) and 450 mg/kg/day naloxegol in rabbits (409 times the human AUC at the maximum recommended human dose) during the period of organogenesis produced no adverse effects on embryo-fetal development. Oral administration of up to 500 mg/kg/day in rats (195 times the maximum recommended human dose based on body surface area) during the period of organogenesis through lactation produced no adverse effects on parturition or the offspring.

8.2 Lactation

There are no data on the presence of naloxegol in human milk, the effects in nursing infants, or the effects on milk production. Naloxegol is present in rat milk (see Data). Because of the potential for adverse reactions, including opioid withdrawal in breastfed infants, advise women that breastfeeding is not recommended during treatment with MOVANTIK.

Data

Following oral administration of naloxegol in lactating rats, concentrations of naloxegol in milk were approximately 3 to 4 fold higher than concentrations of naloxegol in maternal plasma. Naloxegol was detected in plasma from pups.

8.4 Pediatric Use

The safety and effectiveness of MOVANTIK have not been established in pediatric patients.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of MOVANTIK, 11% were 65 and over, while 2% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients; but greater sensitivity of some older individuals cannot be ruled out.

MOVANTIK exposure was higher in elderly healthy Japanese subjects compared to young subjects (see Clinical Pharmacology (12.3)). No dosage adjustment is needed in elderly patients.

8.6 Renal Impairment

Some subjects with creatinine clearance (CLcr) values < 60 mL/minute (i.e., moderate, severe or end-stage renal disease) were shown to exhibit markedly higher systemic exposure of naloxegol compared to subjects with normal renal function. The reason for these high exposures is not understood. However, as the risk of adverse reactions increases with systemic exposure, a lower starting dose of 8.6 mg/day or 150 mg is recommended.

Distribution

No dosage adjustment is required for patients with mild to moderate hepatic impairment (see Clinical Pharmacology (12.3)).

10 OVERDOSAGE

In a clinical study of patients with OIC a daily dose of 50 mg (twice the recommended dosage), administered over 4 weeks, was associated with an increased incidence of GI adverse reactions, such as abdominal pain, diarrhea and nausea. These adverse reactions frequently occurred within 1-2 days after dosing.

No antidote is known for naloxegol. Dialysis was noted to be ineffective as a means of elimination in a clinical study in patients with renal failure.

If a patient on opioid therapy receives an overdose of naloxegol, the patient should be monitored closely for potential evidence of opioid withdrawal symptoms such as chills, rhinorrhea, diaphoresis or reversal of central analgesic effect. Base treatment on the degree of opioid withdrawal symptoms, including changes in blood pressure and heart rate, and on the need for analgesia.
When compared to Caucasian subjects, there is no gender effect on the pharmacokinetics of naloxegol. Gender: approximately 45% and 54% greater than those obtained in young healthy subjects (n=6) following daily oral dosing of 600 mg rifampicin and once daily oral dosing of 240 mg diltiazem (as an extended release formulation) on the pharmacokinetics of 25 mg MOVANTIK were studied following single dosing of the perpetrator drugs. The effects of once daily oral dosing of 400 mg ketoconazole, once [see Drug Interactions (7.1)].

**Drug Interaction Studies**

- **Effect of MOVANTIK on Other Drugs**
  - In vitro studies with clinically relevant concentrations, naloxegol did not show a significant inhibitory effect on the activity of CYP1A2, CYP2C9, CYP2C19, or CYP3A4. Therefore, MOVANTIK is not expected to alter the metabolic clearance of co-administered drugs that are metabolized by these enzymes. Naloxegol is not a significant inhibitor of P-gp, BCRP, OAT1, OAT3, OCT1, OATP1B1 and OATP1B3. In healthy subjects receiving morphine 5 mg/70 kg intravenously, single doses of MOVANTIK ranging from 8 mg to 3000 mg were given concomitantly with 5 to 6 subjects per dose cohort. With increasing MOVANTIK dose, there was no increasing or decreasing trend in morphine exposure compared to morphine administered alone. An analysis of the pooled data indicated that MOVANTIK had no meaningful impact on the systemic exposure of morphine and its major circulating metabolites.

The effect of MOVANTIK on other drugs is minimal. No drug interaction studies have been conducted for MOVANTIK with drugs that alter gastric pH (e.g., antacids, proton-pump inhibitors). Simulations using physiologically based pharmacokinetic modeling, suggested that naloxegol exposures after co-administration of a single oral 25 mg dose of MOVANTIK with a moderate CYP3A inducer efavirenz (400 mg once a day) are similar to those after 12.5 mg MOVANTIK alone.

**Hepatic Impairment**

- slight decreases in AUC of naloxegol were observed in subjects with mild and moderate hepatic impairment (Child-Pugh Classes A and B; n=8 per group) compared to subjects with normal hepatic function (n=8), following administration of a single 25 mg oral dose of MOVANTIK. The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of naloxegol was not evaluated [see Use in Specific Populations (8.7)].

**Renal Impairment**

- When compared to Caucasian subjects, naloxegol AUC was approximately 20% lower in Blacks and C_{max} was approximately 10% lower and 30% higher in Blacks and Asians, respectively.

**Drug Interaction Studies**

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**Effect of Other Drugs on MOVANTIK**

- Naloxegol was metabolized mainly by CYP3A enzymes and is a substrate of P-gp transporter. The effects of co-administered drugs on the pharmacokinetics of naloxegol are summarized in Figure 1 [see Drug Interactions (7.1)]. The effects of once daily oral dosing of 400 mg ketoconazole, once daily oral dosing of 600 mg rifampicin and once daily oral dosing of 240 mg diltiazem (as an extended release formulation) on the pharmacokinetics of 25 mg MOVANTIK were studied following multiple dosing and at steady state exposure of the perpetrator drugs. The effects of 600 mg oral dosing of quinidine and intravenous morphine (5 mg/70 kg) on the pharmacokinetics of 25 mg MOVANTIK were studied following single dosing of the perpetrator drugs.

- When compared to Caucasian subjects, naloxegol AUC was approximately 20% lower in Blacks and C_{max} was approximately 10% lower and 30% higher in Blacks and Asians, respectively.

**Drug Interaction Studies**

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**Hepatic Impairment**

- slight decreases in AUC of naloxegol were observed in subjects with mild and moderate hepatic impairment (Child-Pugh Classes A and B; n=8 per group) compared to subjects with normal hepatic function (n=8), following administration of a single 25 mg oral dose of MOVANTIK. The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of naloxegol was not evaluated [see Use in Specific Populations (8.7)].

**Renal Impairment**

- When compared to Caucasian subjects, naloxegol AUC was approximately 20% lower in Blacks and C_{max} was approximately 10% lower and 30% higher in Blacks and Asians, respectively.
The primary endpoint was response defined as: ≥3 SBMs per week and a change from baseline of ≥1 SBM per week for at least 9 out of the 12 study weeks and 3 out of the last 4 weeks.

There was a statistically significant difference for the 25 mg MOVANTIK treatment group versus placebo for the primary endpoint in Study 1 and Study 2 (see Table 3). Statistical significance for the 12.5 mg treatment group versus placebo was observed in Study 1 but not in Study 2 (see Table 3).

### Table 3. Primary Endpoint: Response* (Studies 1 and 2)

<table>
<thead>
<tr>
<th>Study</th>
<th>Placebo (N = 214)</th>
<th>12.5 mg (N = 213)</th>
<th>25 mg (N = 214)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients responding, n (%)</td>
<td>63 (29%)</td>
<td>87 (41%)</td>
<td>95 (44%)</td>
</tr>
<tr>
<td>Treatment Difference (MOVANTIK-Placebo)</td>
<td>--</td>
<td>11.4%</td>
<td>15.0%</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>--</td>
<td>(2.4%, 20.4%)</td>
<td>(5.9%, 24.0%)</td>
</tr>
<tr>
<td>p-value</td>
<td>--</td>
<td>0.015†</td>
<td>0.001†</td>
</tr>
</tbody>
</table>

* Response defined as: ≥3 SBMs per week and a change from baseline of ≥1 SBM per week for at least 9 out of the 12 study weeks and 3 out of the last 4 weeks.

† Statistical significance: p-values based on the Cochran-Mantel-Haenszel test.

One secondary endpoint in Study 1 and Study 2 was response in laxative users with OIC symptoms. This subgroup comprised 55% and 53% of total patients in these two studies, respectively. These patients (identified using an investigator-administered questionnaire), prior to enrollment, had reported using laxative(s) at least 4 out of the past 14 days with at least one of the following OIC symptoms of moderate, severe or very severe intensity: incomplete bowel movements, hard stool, straining, or sensation of needing to pass a bowel movement but unable to do so. In this subgroup, in Studies 1 and 2, 42% and 50% reported using laxatives on a daily basis. The most frequently reported laxatives used on a daily basis were stool softeners (18% and 24%), stimulants (16% and 18%), and polyethylene glycol (8% and 5%). Use of two laxative classes was reported in 31% and 27% anytime during the 14 days prior to enrolment. The most commonly reported combination was stimulants and stool softeners (10% and 6%). In Study 1, a statistically significantly higher percentage of patients in this subgroup responded with MOVANTIK 12.5 mg compared to placebo (43% vs. 29%; p = 0.03) and with MOVANTIK 25 mg compared to placebo (49% vs. 29%; p = 0.002). In Study 2, a statistically significantly higher percentage of patients in this subgroup responded with MOVANTIK 25 mg compared to placebo (47% vs. 31%; p < 0.01). This secondary endpoint was not tested for MOVANTIK 12.5 mg versus placebo in Study 2 because the primary endpoint was not statistically significant.

Another secondary endpoint was time to first post-dose SBM. The time to first post-dose SBM was significantly shorter with MOVANTIK 25 mg compared to placebo in both Study 1 (p < 0.001) and Study 2 (p < 0.001), and for MOVANTIK 12.5 mg as compared to placebo in Study 1 (p < 0.001). For Study 1, the median times to first post-dose SBM were 6, 20, and 36 hours with MOVANTIK 25 mg, MOVANTIK 12.5 mg, and placebo, respectively. For Study 2, the median times to first post-dose SBM were 12 and 37 hours with MOVANTIK 25 mg and placebo, respectively. These analyses do not include the results for MOVANTIK 12.5 mg versus placebo in Study 2 because the primary endpoint was not statistically significant. In the two studies, 61-70% and 58% of patients receiving MOVANTIK 25 mg and MOVANTIK 12.5 mg, respectively, had an SBM within 24 hours of the first dose.

A third secondary endpoint was an evaluation of change from baseline between the treatment groups for mean number of days per week with at least 1 SBM but no more than 3 SBMs. There was a significant difference in number of days per week with 1 to 3 SBMs per day on average over 12 weeks between MOVANTIK 25 mg (Study 1 and Study 2) and MOVANTIK 12.5 mg (Study 1) and placebo.

### 16 HOW SUPPLIED/STORAGE AND HANDLING

MOVANTIK (naloxegol) tablets, for oral use

- NDC 0310-1970-30: 25 mg, bottle of 30 tablets
- NDC 0310-1970-90: 25 mg, bottle of 90 tablets
- NDC 0310-1969-39: 12.5 mg, unit dose blister carton of 100 tablets (for HUD only)
- NDC 0310-1970-30: 25 mg, bottle of 30 tablets
- NDC 0310-1970-90: 25 mg, bottle of 90 tablets
- NDC 0310-1970-39: 25 mg, unit dose blister carton of 100 tablets (for HUD only)

**Storage**

Store MOVANTIK at 20-25°C (68-77°F). Excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

### 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

**Administration**

Advise patients to:
- 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 three days.
- Take MOVANTIK on an empty stomach at least 1 hour prior to the first meal of the day or 2 hours after the meal.
- Discontinue MOVANTIK if treatment with the opioid pain medication is also discontinued.
- Avoid consumption of grapefruit or grapefruit juice during treatment with MOVANTIK.
- Inform their healthcare provider if their opioid pain medication is discontinued.
- Inform their healthcare provider if they are unable to tolerate MOVANTIK, so a dosage adjustment can be considered.

If patients are unable to swallow the MOVANTIK tablet whole, the tablet can be crushed to a powder, mixed with water and administered orally or via a nasogastric (NG) tube, as described in the Medication Guide.

**Drug Interactions**

Advise patients to tell their healthcare provider when they start or stop taking any concomitant medications. Strong CYP3A4 inhibitors (e.g., clarithromycin, ketoconazole) are contraindicated with MOVANTIK, and other CYP3A4 enzyme modulating drugs can alter MOVANTIK exposure [see Contraindications (4) and Drug Interactions (7.1)].

**Opioid Withdrawal**

Advise patients that clusters of symptoms consistent with opioid withdrawal may occur while taking MOVANTIK, including sweating, chills, diarrhea, abdominal pain, anxiety, irritability, and yawning. Inform patients taking methadone as therapy for their pain condition that they may be more likely to have gastrointestinal adverse reactions such as abdominal pain and diarrhea that may be related to opioid withdrawal, than patients receiving other opioids [see Warnings and Precautions (5.1)].

**Severe Abdominal Pain and/or Diarrhea**

Advise patients that symptoms may occur after starting treatment. The patient should discontinue MOVANTIK and contact their healthcare provider if they develop severe abdominal pain and/or diarrhea [see Warnings and Precautions (5.2)].

**Gastrointestinal Perforation**

Advise patients to discontinue MOVANTIK and promptly seek medical attention if they develop unusually severe, persistent or worsening abdominal pain [see Warnings and Precautions (5.3)].

**Pregnancy**

Advise females of reproductive potential, who become pregnant or are planning to become pregnant that the use of MOVANTIK during pregnancy may precipitate opioid withdrawal in the pregnant woman and the fetus [see Use in Specific Populations (8.1)].

**Lactation**

Advise females that breastfeeding is not recommended during treatment with MOVANTIK [see Use in Specific Populations (8.2)].

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# MEDICATION GUIDE

**MOVANTIK® (mo-van-tic)**
(naloxegol)
tablets, for oral use

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Read this Medication Guide before you start taking MOVANTIK and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

## What is the most important information I should know about MOVANTIK?

MOVANTIK may cause serious side effects, including:

- **Opioid withdrawal.** You may have symptoms of opioid withdrawal during treatment with MOVANTIK including sweating, chills, diarrhea, stomach pain, anxiety, irritability, and yawning. If you take methadone to treat your pain, you may be more likely to have stomach pain and diarrhea than people who do not take methadone. Tell your health care provider if you have any of these symptoms.

- **Severe stomach pain or diarrhea, or both severe stomach pain and diarrhea.** Severe stomach pain and diarrhea can happen when you take MOVANTIK. These problems can happen within a few days after you start taking MOVANTIK and can lead to hospitalization. Stop taking MOVANTIK and call your healthcare provider right away if you have severe stomach pain or diarrhea, or both severe stomach pain and diarrhea.

- **Tear in your stomach or intestinal wall (perforation).** Stomach pain that is severe can be a sign of a serious medical condition. If you have stomach pain that gets worse or does not go away, stop taking MOVANTIK and get emergency medical help right away.

## What is MOVANTIK?

MOVANTIK is a prescription medicine used to treat constipation that is caused by prescription pain medicines called opioids, in adults with long-lasting (chronic) pain that is not caused by active cancer.

It is not known if MOVANTIK is safe and effective in children.

## Who should not take MOVANTIK?

Do not take MOVANTIK if you:

- have a bowel blockage (intestinal obstruction) or have a history of bowel blockage.
- are allergic to MOVANTIK or any of the ingredients in MOVANTIK. See the end of this Medication Guide for a complete list of ingredients in MOVANTIK.

MOVANTIK can interact with certain other medicines and cause side effects, including opioid withdrawal symptoms such as sweating, chills, diarrhea, stomach pain, anxiety, irritability, and yawning. Tell your healthcare provider or pharmacist before you start or stop any medicines during treatment with MOVANTIK.

## What should I tell my healthcare provider before taking MOVANTIK?

Before you take MOVANTIK, tell your healthcare provider about all of your medical conditions, including if you:

- have any stomach or bowel (intestines) problems, including stomach ulcer, Crohn’s disease, diverticulitis, cancer of the stomach or bowel, or Ogilvie’s syndrome.
- have kidney problems.
- have liver problems.
- are pregnant or plan to become pregnant. Taking MOVANTIK during pregnancy may cause opioid withdrawal symptoms in you or your unborn baby. Tell your healthcare provider right away if you become pregnant during treatment with MOVANTIK.
- are breastfeeding or plan to breastfeed. It is not known if MOVANTIK passes into your breast milk.
- are taking MOVANTIK while you are breastfeeding may cause opioid withdrawal in your baby. You and your healthcare provider should decide if you will take MOVANTIK or breastfeed. You should not breastfeed if you take MOVANTIK.

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Other medicines may affect the way MOVANTIK works.

## How should I take MOVANTIK?

- Take MOVANTIK exactly as your healthcare provider tells you.
- Take your prescribed dose of MOVANTIK one time each day, on an empty stomach, at least 1 hour before your first meal of the day or 2 hours after the meal.

**If you cannot swallow MOVANTIK tablets whole,** MOVANTIK can be mixed with water and taken by mouth or given through a nasogastric (NG) tube. To take MOVANTIK by mouth:

- crush the tablet to a powder
- place your dose of MOVANTIK in a glass that contains 4 ounces (120 mL) of water and stir
- swallow MOVANTIK and water mixture right away
- add 4 more ounces (120 mL) of water to the glass and drink right away, to make sure that you take your full dose of MOVANTIK.

**If you cannot swallow MOVANTIK tablets and have a nasogastric (NG) tube,** MOVANTIK may be given as follows:

- draw up 1 ounce (30 mL) of water into a 60 mL syringe and flush the NG tube
- crush the tablet to a powder
- place your dose of MOVANTIK in a container and mix with approximately 2 ounces (60 mL) of water
- draw up the MOVANTIK and water into the 60 mL syringe and give the mixture through the NG tube
- add approximately 2 ounces (60 mL) of water to the same container you used to prepare your dose of MOVANTIK
- draw up the water using the same 60 mL syringe and use all the water to flush the NG tube and any remaining medicine from the NG tube into the stomach.
• Stop taking other laxatives before you start treatment with MOVANTIK. Your healthcare provider may prescribe other laxatives if MOVANTIK does not work after 3 days of treatment.
• MOVANTIK has been shown to be effective in people who have taken opioid pain medicines for at least 4 weeks.
• Tell your healthcare provider if you stop taking your opioid pain medicine. If you stop taking your opioid pain medicine, you should also stop taking MOVANTIK.
• If you take too much MOVANTIK, call your healthcare provider or go to the nearest emergency room right away.

What should I avoid while taking MOVANTIK?
• Avoid eating grapefruit or drinking grapefruit juice during treatment with MOVANTIK.

What are the possible side effects of MOVANTIK?
See “What is the most important information I should know about MOVANTIK?”
The most common side effects of MOVANTIK include: stomach (abdomen) pain, diarrhea, nausea, gas, vomiting, and headache.
Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of MOVANTIK.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store MOVANTIK?
• Store MOVANTIK at room temperature between 68°F to 77°F (20°C to 25°C).
• Safely throw away medicine that is out of date or that you no longer need.
Keep MOVANTIK and all medicines out of the reach of children.

General information about the safe and effective use of MOVANTIK
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use MOVANTIK for a condition for which it was not prescribed. Do not give MOVANTIK to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about MOVANTIK that is written for health professionals.

What are the ingredients in MOVANTIK?
Active ingredient: naloxegol oxalate
Inactive ingredients: The tablet core contains mannitol, cellulose microcrystalline, croscarmellose sodium, magnesium stearate, and propyl gallate. The tablet coat contains hypromellose, titanium dioxide, polyethylene glycol, iron oxide red, and iron oxide black.

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