PRODUCT MONOGRAPH

Pr MOVANTIK®

naloxegol tablet

12.5 mg and 25 mg naloxegol as naloxegol oxalate

peripherally acting μ-opioid receptor antagonist

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablets, 12.5 mg and 25 mg	None. *For a complete listing of nonmedicinal ingredients see DOSAGE FORMS, COMPOSITION AND PACKAGING.*

INDICATIONS AND CLINICAL USE

MOVANTIK (naloxegol oxalate) is indicated for the treatment of opioid-induced constipation (OIC) in adult patients with non-cancer pain who have had an inadequate response to laxative(s).

Pediatrics (<18 years of age): The safety and efficacy of MOVANTIK in pediatric patients below 18 years of age has not been established and is not indicated for use in this patient population.

CONTRAINDICATIONS

MOVANTIK (naloxegol oxalate) is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container, or to any other opioid antagonist. For a complete listing of ingredients, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.

- Patients with known or suspected gastrointestinal obstruction or in patients at increased risk of recurrent obstruction, due to the potential for gastrointestinal perforation (see WARNINGS AND PRECAUTIONS, Gastrointestinal).

- Patients concomitantly receiving strong CYP3A4 inhibitors (e.g., ketoconazole, voriconazole, clarithromycin, protease inhibitors such as ritonavir), due to significant increase in exposure to naloxegol (see DRUG INTERACTIONS).

WARNINGS AND PRECAUTIONS

General

Opioid withdrawal syndrome: Cases of opioid withdrawal syndrome have been reported in patients treated with MOVANTIK. Opioid withdrawal syndrome is a cluster of three or more of the following signs or symptoms: hyperhidrosis, dysphoric mood, nausea or vomiting, muscle aches, lacrimation or rhinnorrhea, pupillary dilation or piloerection or sweating, diarrhea, yawning, fever or insomnia. If opioid withdrawal syndrome is suspected the patient should discontinue MOVANTIK and contact their healthcare professional (see Neurologic).

Concurrent methadone use: Patients receiving methadone for their pain in clinical trials had a higher frequency of gastrointestinal adverse events (such as abdominal pain and diarrhea) than patients not receiving methadone and, in a few cases, symptoms suggestive of opioid withdrawal when receiving MOVANTIK 25 mg were observed.

Interactions: Concomitant use of MOVANTIK with strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) can significantly reduce exposure to naloxegol and should generally be avoided (see DRUG INTERACTIONS).

The concomitant use of moderate CYP3A4 inhibitors (e.g. diltiazem, verapamil, erythromycin) should be avoided with MOVANTIK, since the systemic exposure to naloxegol is increased. If this concomitant use is considered absolutely necessary by the physician, the possible benefits of MOVANTIK must clearly outweigh the risk of toxicity due to increase in systemic exposure to MOVANTIK, and it is recommended to use a daily MOVANTIK dose of 12.5 mg with close monitoring for signs of adverse events (e.g., opioid withdrawal syndrome and/or reversal of analgesia). See DRUG INTERACTIONS; DOSAGE AND ADMINISTRATION, Special Populations.

Concomitant consumption of grapefruit (a CYP3A4 inhibitor) or grapefruit juice while taking MOVANTIK should be avoided.

Concomitant use of strong CYP3A4 inhibitors is contraindicated (see CONTRAINDICATIONS and DRUG INTERACTIONS).

Cardiovascular

Patients with cardiovascular conditions: MOVANTIK was not studied in the clinical trial program in patients who had a recent history of myocardial infarction within 6

months, symptomatic congestive heart failure, overt cardiovascular disease or patients with a QT interval of ≥ 500msec. MOVANTIK should be used with caution in these patients. A QTc study performed with naloxegol in healthy volunteers did not indicate any prolongation of the QT interval at the intended therapeutic dose (see ACTION AND CLINICAL PHARMACOLOGY, Mechanism of Action and Pharmacodynamics).

Gastrointestinal

Potential for gastrointestinal perforation: Cases of gastrointestinal perforation have been reported in the post-marketing setting including fatal cases when naloxegol was used in patients who were at an increased risk of gastrointestinal perforation. Naloxegol must not be used in patients with known or suspected gastrointestinal obstruction or in patients at an increased risk of recurrent obstruction, or in patients with underlying cancer who are at heightened risk of gastrointestinal perforation. Caution with regards to the use of MOVANTIK should be exercised in patients with any condition which might result in impaired integrity of the gastrointestinal tract wall (e.g., severe peptic ulcer disease, Crohn's Disease, active or recurrent diverticulitis, infiltrative gastrointestinal tract malignancies or peritoneal metastases) taking into account the overall benefit-risk profile for a given patient. Patients should be advised to discontinue MOVANTIK therapy and promptly notify their physician if they develop unusually severe or persistent abdominal pain.

Severe abdominal pain and/or severe diarrhea: MOVANTIK may cause severe abdominal pain and/or severe diarrhea. Reports of severe abdominal pain and/or severe diarrhea have been observed in clinical trials with the 25 mg dose, typically occurring shortly after initiation of treatment. There was a higher incidence of severe and/or serious adverse events of abdominal pain in patients taking the 25 mg dose compared to placebo (5.6% for naloxegol 25 mg vs. 0.9% placebo) and diarrhea (1.6% for naloxegol 25 mg vs. 1.1% for placebo). Patients should be advised to discontinue therapy if severe symptoms occur, and promptly report severe, persistent or worsening symptoms to their physician.

Hepatic

Severe hepatic impairment: MOVANTIK has not been studied in patients with severe hepatic impairment (Child-Pugh Class C); therefore, the use of MOVANTIK is not recommended in such patients.

Neurologic

Disruptions of the blood-brain barrier: Patients with clinically important disruptions to the blood-brain barrier may be at higher risk for naloxegol entry into the CNS, and opioid withdrawal syndrome or reversal of analgesia. In these patients, MOVANTIK should only be used if the potential benefits clearly outweigh the risks of MOVANTIK, with observation for potential CNS effects, such as Symptoms of opioid withdrawal or reversal of analgesia.

Renal

Renal impairment: As a few patients may experience higher than normal exposure to naloxegol, treatment with MOVANTIK should be discontinued if side effects impacting

tolerability occur. The starting daily dose for patients with moderate, severe or end-stage renal impairment is 12.5 mg. If needed and if the 12.5 mg dose is well tolerated, daily the dose can be increased to 25 mg (see DOSAGE AND ADMINISTRATION, Special Populations; ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

Psychomotor Impairment

No studies have been conducted to assess ability to drive while taking MOVANTIK. MOVANTIK is not expected to have any meaningful influence on the ability to drive or use machines.

Special Populations

Pregnant women: There are no adequate clinical data on the use of MOVANTIK in pregnant women.

The use of MOVANTIK during pregnancy is not recommended due to the risk of opioid withdrawal for the fetus (immature blood brain barrier).

Animal studies do not indicate harmful effects with respect to pregnancy, embryonic/fetal development, parturition or postnatal development at exposures in excess of 70 times the human therapeutic exposure. Naloxegol had no effect on fertility in animals (see Part II: TOXICOLOGY).

Nursing women: It is unknown whether naloxegol is excreted in human breast milk, however, naloxegol is excreted in rat milk and absorbed in bursing rat pups. Therefore due to the possible risk of opioid withdrawal in infants, the use of MOVANTIK in nursing women is not recommended.

Pediatrics (<18 years of age): The safety and efficacy of MOVANTIK in pediatric patients below 18 years of age have not been established and is not indicated in this patient population.

Geriatrics (≥65 years of age): Some increase in naloxegol systemic exposure was noted in some elderly subjects (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions). No dose adjustment is recommended for the elderly (see ADVERSE REACTIONS; DOSAGE AND ADMINISTRATION, Special Populations).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Across all Phase II/III clinical studies, approximately 1500 patients with non-cancer pain opioid-induced constipation (OIC) were exposed to MOVANTIK. However, only Phase III clinical trials are discussed for safety. The following table summarises the Phase III studies providing the main safety data.

Table 1 Main Phase III clinical studies providing data for the safety evaluation of naloxegol

Study	Type of study	Treatment Duration	Naloxegol and comparator treatment groups	Exposure median time (days)	Patients with exposure ≥ 12 weeks
KODIAC 4 and KODIAC 5 (pooled)	Double-blind, randomized, Placebo-controlled (safety and efficacy)	12 weeks	Placebo (N=444)	85	72.3%
			NGL 12.5 mg QD (N=441)	85	72.1%
			NGL 25 mg QD (N=446))	85	70.4%
				Exposure median time (days)	**Patients with exposure ≥ 52 weeks**
KODIAC 8	Open label, long-term safety and tolerability study	52 weeks	Usual Care [a] (N=270)	360	69.3%
			NGL 25 mg QD (N=534)	358	59.4%

[a] flexible laxative treatment regimen determined by the Investigator according to his/her best clinical judgement. Some of the patients continued from KODIAC 5 and KODIAC 7.

Abbreviations: NGL naloxegol

An additional extension study (KODIAC 7) included 291 patients who were rolled over from the KODIAC 4 study (97 treated with MOVANTIK 25 mg, 94 with MOVANTIK 12.5 mg, and 100 with placebo). Overall 188 patients were exposed to >24-week treatment (63 patients with MOVANTIK 25 mg, 56 with MOVANTIK 12.5 mg, and 63 with placebo groups).

In the two 12-week pivotal placebo-controlled Phase III studies (KODIAC 4 and KODIAC 5), 446 patients received MOVANTIK 25 mg, 441 patients received MOVANTIK 12.5 mg, and 444 received placebo. Overall, treatment-emergent adverse events (AEs) occurred in 52.4%, 63.5% and 51.1% of patients treated with MOVANTIK 12.5 mg, MOVANTIK 25 mg and placebo respectively. The most commonly reported treatment-emergent AEs (reported regardless of causality) with MOVANTIK (≥5%) were abdominal pain, diarrhea, nausea and flatulence (see Table 2). Frequencies and patterns of AEs in the 12-week blinded safety extension study (KODIAC 7) and in the 52-week long-term open-label safety study (KODIAC 8) were generally consistent with those in the 12-week studies, as were the patient's reasons for requiring opioid medication. Most AEs reported with MOVANTIK were mild to moderate in intensity.

The proportion of patients with discontinuation due to AEs (DAEs) in KODIAC 4 and KODIAC 5 was higher in the MOVANTIK 25 mg group (10.3%) than in the MOVANTIK 12.5 mg (4.8%) and placebo (5.4%) groups. The most common DAEs were due to gastrointestinal AEs: diarrhea, abdominal pain and nausea, and the higher rate of DAEs in the 25 mg group appeared to be driven predominantly by treatment differences in the incidence of diarrhea and abdominal pain DAEs. The incidence and pattern of DAEs in the MOVANTIK 25 mg group in KODIAC 8 (52-week study) was comparable to those seen in the 12-week studies.

The incidence of Serious Adverse Events (SAEs) at any time during the 12-week studies was 5.7%, 3.4% and 5.2% in the MOVANTIK 12.5 mg, MOVANTIK 25 mg and placebo groups respectively. The incidence of SAEs in KODIAC 8 was 9.6% in the MOVANTIK 25 mg group and 11.1% in the standard of care group.

There was a higher incidence of severe and/or serious adverse events of abdominal pain in patients taking the 25 mg dose compared to placebo (5.6% for naloxegol 25 mg vs. 0.9% placebo) and diarrhea (1.6% for naloxegol 25 mg vs. 1.1% for placebo).

Uncommon AEs of opioid withdrawal syndrome were reported (see "Opioid Withdrawal" at the end of "Clinical Trial Adverse Drug Reactions" section).

MOVANTIK (naloxegol oxalate) at doses up to 25 mg once daily was generally well tolerated with most of the adverse events being mild to moderate in intensity in LIR patients with opioid-induced constipation (OIC), in clinical studies up to 52 weeks of treatment.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The most commonly reported (≥5%) adverse drug reactions for MOVANTIK 25 mg across all naloxegol clinical studies were abdominal pain (20.6%, the majority of such events were graded as mild to moderate), diarrhea (11.6%), nausea (9.3%), headache (7.0%), flatulence (6.6%) and vomiting (5.2%). Other adverse drug reactions at a lower frequency were nasopharyngitis (4.3%) and hyperhidrosis (3.2%).

Table 2 presents treatment-emergent AEs (regardless of causality) that occurred in patients from two replicate, randomized, double-blind, placebo-controlled studies of 12 weeks duration (KODIAC 4 and KODIAC 5) in ≥2% of patients treated with MOVANTIK (12.5 mg and 25 mg) where the incidence in patients treated with MOVANTIK was greater than the incidence in placebo-treated patients.

Table 2 **Adverse Events, Regardless of Causality, Occurring in ≥2% of patients and reported more frequently with MOVANTIK than Placebo in OIC Patients[a] with non-cancer pain[b] (KODIAC 4 and KODIAC 5 - Pooled 12 Weeks Duration)**

Body System Preferred term	Placebo (N=444)	NGL 12.5 mg (N=441)	NGL 25 mg (N=446)
Patients with any AE	227 (51.1)	231 (52.4)	283 (63.5)
Gastrointestinal disorders			
Abdominal pain	25 (5.6)	43 (9.8)	71 (15.9)
Diarrhea	19 (4.3)	25 (5.7)	41 (9.2)
Nausea	20 (4.5)	29 (6.6)	36 (8.1)
Flatulence	11 (2.5)	13 (2.9)	26 (5.8)
Vomiting	13 (2.9)	10 (2.3)	20 (4.5)
Abdominal pain upper	7 (1.6)	8 (1.8)	17 (3.8)
Abdominal distension	9 (2.0)	11 (2.5)	11 (2.5)
Nervous system disorders			
Headache	12 (2.7)	17 (3.9)	20 (4.5)
Dizziness	9 (2.0)	11 (2.5)	3 (0.7)
Musculoskeletal and connective tissue disorders			
Back pain	9 (2.0)	12 (2.7)	19 (4.3)
Pain in extremity	3 (0.7)	5 (1.1)	10 (2.2)
Skin and subcutaneous tissue disorders			
Hyperhidrosis	1 (0.2)	2 (0.5)	13 (2.9)
General disorders and administration site conditions			
Fatigue	6 (1.4)	7 (1.6)	10 (2.2)
Infection and Infestations			
Sinusitis	6 (1.4)	6 (1.4)	10 (2.2)
Nasopharyngitis	1 (0.2)	5 (1.1)	9 (2.0)
Injury, poisoning and procedural complications			
Fall	8 (1.8)	9 (2.0)	4 (0.9)

[a] Patients with events in ≥1 preferred term are counted once in each of those preferred terms. AEs that started on or after the first dose of investigational product through end of study are included.

[b] Studies included patients with back pain (56.5%), other (18.3%), arthritis (9.8%), fibromyalgia (5.6%), joint pain (4.4%), neuralgia (2.3%) pain syndrome (1.7%) and headache/migraine (1.2%).

Abbreviations: NGL naloxegol

A total of 147 (11%) elderly patients ≥65 years of age with OIC were treated with MOVANTIK in the 12-week Phase III studies. The most common AEs reported in the elderly group were similar to the younger age group. No clinically significant difference was noted as compared to adult patients <65 years of age.

The frequencies and patterns of AEs in patients with baseline laxative inadequate responder (LIR) status were generally comparable to that of the overall safety population.

In the 52-week study (KODIAC 8), the adverse event profile was generally consistent with the short-term studies and there were no important or unexpected differences in the safety and tolerability between the MOVANTIK 25 mg group and the usual care group. The proportion of patients who reported at least 1 adverse event was 72% for the usual care control group, and 82% for the MOVANTIK 25 mg group.

Less Common Clinical Trial Treatment Emergent Adverse Events

Treatment emergent AEs (regardless of causality) that were reported in <2% of patients treated with MOVANTIK and in at least 2 patients in any MOVANTIK dose group and in frequency greater than placebo in the two replicate Phase III 12-week studies are listed below by body system:

Cardiac disorders: palpitations, ventricular extrasystoles
Eye disorders: dry eye
Gastrointestinal disorders: abdominal discomfort, abdominal pain lower, abdominal tenderness, dry mouth, eructation, gastritis, gastroesophageal reflux disease, gastrointestinal pain, toothache
General disorders and administration site conditions: asthenia, opioid withdrawal syndrome, feeling jittery, influenza like illness, local swelling, localized edema, peripheral edema, pyrexia
Infections and infestations: bronchitis, cellulitis, cystitis, fungal infection, gastroenteritis, gastroenteritis viral, herpes zoster, oral herpes, otitis media, pneumonia, tooth abscess
Injury, poisoning and procedural complications: accidental overdose, animal bite, arthropod bite, contusion, excoriation
Investigations: blood bicarbonate decreased, blood creatinine increased, blood glucose increased, blood pressure increased, blood thyroid stimulating hormone increased, blood urea increased, hematocrit decreased, hemoglobin decreased, liver function test abnormal, weight decreased, weight increased
Metabolism and nutrition disorders: decreased appetite, dehydration, hypercholesterolemia, hyperlipidemia, vitamin D deficiency
Musculoskeletal and connective tissue disorders: arthritis, flank pain, musculoskeletal chest pain, myalgia, neck pain, osteoarthritis, osteopenia, synovial cyst
Nervous system disorder: migraine, paraesthesia, syncope, tremor
Psychiatric disorders: anxiety, nightmare, panic attack
Renal and urinary disorders: acute renal failure, micturition urgency, pollakiuria
Respiratory, thoracic and mediastinal disorders: asthma, cough, nasal congestion, oropharyngeal pain, paranasal sinus hypersecretion, respiratory tract congestion, rhinorrhea,

yawning
Skin and subcutaneous tissue disorders: cold sweat, contact dermatitis, erythema, urticaria
Vascular disorders: flushing, hot flush, hypertension, hypotension

Opioid Withdrawal
Possible opioid withdrawal, defined as ≥3 adverse reaction potentially related to opioid withdrawal that occurred on the same day and were not all related to the gastrointestinal system, occurred in less than 1% (1/444) of placebo subjects, 1% (5/441) receiving MOVANTIK 12.5 mg, and 3% (14/446) receiving MOVANTIK 25 mg in KODIAC 4 and KODIAC 5 regardless of maintenance opioid treatment. Symptoms included but were not limited to hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, irritability, and yawning. Patients receiving methadone as therapy for their pain condition were observed in KODIAC 4 and KODIAC 5 to have a higher frequency of gastrointestinal adverse reactions than patients receiving other opioids [39% (7/18) vs. 26% (110/423) in the 12.5 mg group; 75% (24/32) vs. 34% (142/414) in the 25 mg group].

Abnormal Hematologic and Clinical Chemistry Findings

Refer to the Less Common Clinical Trial Treatment Emergent Adverse Events section under *Investigations* and *Metabolism and nutritional disorders* for information on abnormal hematologic and clinical chemistry findings.

Post-Market Adverse Reactions

The following adverse drug reactions were reported during post-marketing surveillance: gastrointestinal perforation (in patients with increased risk factors for gastrointestinal perforation) and hypersensitivity. Adverse drug reactions are presented by MedDRA System Organ Class in order by preferred term.

DRUG INTERACTIONS

Overview

Naloxegol is a sensitive substrate of CYP3A4 enzyme and a substrate of P-glycoprotein (P-gp) transporter, and CYP3A4 is the major CYP enzyme responsible for the metabolism of naloxegol.

Concomitant use with dual P-gp/strong or moderate CYP3A4 inhibitors, or strong CYP3A4 inhibitors significantly increases naloxegol plasma concentrations. Conversely, concomitant use with strong CYP3A4 inducers or dual P-gp/strong CYP3A4 inducers results in decreased plasma concentrations of naloxegol and should generally be avoided.

Drug-Drug Interactions

Strong CYP3A4 inhibitors
Concomitant use of ketoconazole significantly increased the naloxegol AUC and C_{max} to 12.9- and 9.6-fold, respectively. Therefore, the concomitant use of strong inhibitors (e.g., clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, or protease inhibitors such as ritonavir) is contraindicated with MOVANTIK (see CONTRAINDICATIONS).

Moderate CYP3A4 inhibitors
Concomitant use of diltiazem significantly increased the naloxegol AUC and C_{max} to 3.4- and 2.9-fold, respectively. Therefore, the concomitant use of moderate CYP3A4 inhibitors (e.g. diltiazem, verapamil, erythromycin) should be avoided with MOVANTIK. If this concomitant use is considered absolutely necessary by the physician, the possible benefits of MOVANTIK must clearly outweigh the risk of toxicity due to increase in naloxegol systemic exposure, and it is recommended to use a daily MOVANTIK dose of 12.5 mg with close monitoring for signs of adverse events (e.g., opioid withdrawal syndrome and/or reversal of analgesia).

Weak CYP3A4 inhibitors
Concomitant use of quinidine significantly increased the naloxegol AUC and C_{max} to 1.4- and 2.5-fold respectively. Therefore, the daily dose of MOVANTIK when used concomitantly with a weak CYP3A4 inhibitor (e.g., quinidine or cimetidine) should be 12.5 mg.

Strong CYP3A4 inducers
Concomitant use of rifampin significantly decreased the naloxegol AUC and C_{max} by 89% and 76%, respectively. Therefore, the use of MOVANTIK concomitantly with a strong CYP3A4 inducer (e.g., carbamazepine, phenytoin or St. John's Wort) is not recommended.

Dual P-gp/CYP3A4 inhibitor
Dosing recommendations for MOVANTIK used concomitantly with drug products causing both CYP3A4 and P-gp inhibition should be based on CYP3A4 status (strong, moderate or weak, as described in the previous related paragraphs).

Other μ-opioid receptor antagonists: Given the mode of action of naloxegol, as a peripheral μ-opioid receptor antagonist, it should not be concomitantly taken with any other opioid antagonists (e.g., naltrexone, naloxone) due to the potential for an additive effect of opioid receptor antagonism and an increased risk of opioid withdrawal.

In *in vitro* studies with naloxegol found no significant inhibitory effect on the activity of CYP1A2, CYP2C9, CYP2D6, CYP3A4 or CYP2C19, nor induction effect on the activity of CYP1A2, CYP2B6 or CYP3A4 were observed. Therefore, naloxegol 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, OCT2, OATP1B1 or OATP1B3.

In a study conducted in healthy subjects, naloxegol did not meaningfully alter the pharmacokinetics of morphine and its major circulating metabolites.

Drug-Food Interactions

A high-fat high-calorie meal increased the extent of naloxegol absorption by 45% as measured by the AUC and the rate of naloxegol absorption by 30% as measured by the C_{max}. MOVANTIK should be taken in the morning on an empty stomach at least 1 hour prior to the first meal of

the day or 2 hours post-meal (see DOSAGE AND ADMINISTRATION, Dosing Considerations; ACTION AND CLINICAL PHAMACOLOGY, Pharmacokinetics).

Grapefruit juice has been classified as a CYP3A4 inhibitor. Concomitant consumption of grapefruit or grapefruit juice while taking MOVANTIK should be avoided (see WARNINGS AND PRECAUTIONS, General).

Drug-Herb Interactions

Concomitant use of St. John's wort may lead to significant decrease in naloxegol exposure and, therefore, should be avoided (see WARNINGS AND PRECAUTIONS, General; DRUG INTERACTIONS, Drug-Drug Interactions).

Drug-Laboratory Interactions

Interactions with laboratory tests have not been studied.

DOSAGE AND ADMINISTRATION

Dosing Considerations

MOVANTIK (naloxegol oxalate) should be taken in the morning on an empty stomach at least 1 hour prior to the first meal of the day or 2 hours post-meal (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

For patients who are unable to swallow the tablet whole, the MOVANTIK tablet can be crushed to a powder and mixed in half of a glass of room temperature non-carbonated water (120 ml) and drunk immediately. The glass should then be rinsed with a further half glass of room temperature non-carbonated water (120 ml) and the contents drunk. The mixture can also be administered via a nasogastric tube (CH8 or greater). When administered via a nasogastric tube a total water volume of 240 ml should be used. The patient should be instructed to perform the following steps:

1. Flush the NG tube with 1 ounce (30 mL) of water using a 60 mL syringe.
2. Crush the tablet to a powder in a container and mix with approximately 2 ounces (60mL) of water.
3. Draw up the mixture using the 60 mL syringe and administer the syringe contents through the NG tube.
4. Add approximately 2 ounces (60 mL) of water to the same container used to prepare the 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.

When MOVANTIK therapy is initiated, it is recommended that all currently used maintenance laxative therapy should be stopped, until clinical effect of MOVANTIK is determined.

Recommended Dose and Dosage Adjustment

The recommended dose of MOVANTIK is 25 mg once daily.

Special Populations

Pediatrics (<18 years of age): MOVANTIK is not indicated in children.

Geriatrics (≥65 years of age): No dose adjustment for MOVANTIK is recommended for the elderly (see WARNINGS AND PRECAUTIONS, Special Populations; ADVERSE REACTIONS; ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

Renal impairment: The starting dose for patients with moderate, severe, or end-stage renal impairment is 12.5 mg. The dose can be increased to 25 mg if the 12.5 mg dose is well tolerated. As a few patients may experience higher than normal exposure to naloxegol, treatment with MOVANTIK should be discontinued if side effects impacting tolerability occur (see WARNINGS AND PRECAUTIONS, Renal; ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

Hepatic impairment: No dose adjustment for MOVANTIK is required for patients with mild to moderate hepatic impairment (Child-Pugh Class A and B) (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions). Safety and efficacy of MOVANTIK in patients with severe hepatic impairment (Child-Pugh Class C) have not been established; therefore, the use of MOVANTIK is not recommended in such patients (see WARNINGS AND PRECAUTIONS, Hepatic).

CYP3A4 and P-glycoprotein transporters (P-gp) modulators: Concomitant use with strong CYP3A4 inhibitors (e.g., ketoconazole, voriconazole, clarithromycin, protease inhibitors such as ritonavir) can significantly increase exposure to naloxegol and is contraindicated (see CONTRAINDICATIONS; DRUG INTERACTIONS).

Concomitant use with strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) can significantly reduce exposure to naloxegol and should generally be avoided (see WARNINGS AND PRECAUTIONS, General; DRUG INTERACTIONS).

Concomitant use of moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, erythromycin) should be avoided with MOVANTIK. If this concomitant use is considered absolutely necessary by the physician, the possible benefits of MOVANTIK must clearly outweigh the risk of toxicity due to increase in naloxegol systemic exposure, and it is recommended to use a daily MOVANTIK dose of 12.5 mg with close monitoring for signs of adverse events (e.g., opioid withdrawal syndrome and/or reversal of analgesia) (see DRUG INTERACTIONS).

The dose of MOVANTIK should be decreased to 12.5 mg once daily when it is concomitantly used with weak CYP3A4 inhibitors (e.g., quinidine, cimetidine) (see DRUG INTERACTIONS).

Dosing recommendations for MOVANTIK used concomitantly with therapeutic products causing both CYP3A4 and P-gp inhibition should be based on CYP3A4 status (strong,

moderate or weak, as described in the previous related paragraphs) (see DRUG INTERACTIONS).

Missed Dose

If a patient misses a dose 12 hours or more before the next scheduled dose, the patient should take the missed tablet immediately and then take the next scheduled dose at the normal time.

If a patient misses a dose less than 12 hours before the next scheduled dose, the patient should skip the missed dose and then take the next scheduled dose at the normal time. Patients should be instructed not to take a double dose to make up for a forgotten tablet.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Signs and Symptoms

In a clinical study of patients with OIC, a daily dose of 50 mg was associated with an increased incidence of intolerable gastrointestinal adverse reactions (primarily abdominal pain, diarrhea and/or nausea).

Treatment

There is currently no known antidote to reverse the effect of MOVANTIK (naloxegol oxalate). 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 MOVANTIK, the patient should be monitored closely for potential evidence of opioid withdrawal symptoms or reversal of central analgesic effect. In cases of known or suspected overdose of MOVANTIK, symptomatic treatment as well as monitoring of vital functions should be performed.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action and Pharmacodynamics

Physiological effects of opioids in the gastrointestinal tract are caused by binding at opioid receptors within the enteric nervous system and include decreased motility, decreased secretions and increased absorption of fluid from intestines, which may cause constipation in 40-90% of individuals who take opioids.

MOVANTIK (naloxegol oxalate) is a peripherally acting μ-opioid receptor antagonist (PAMORA). Naloxegol is a PEGylated derivative of the μ-opioid receptor antagonist naloxone and antagonizes opioid binding at the peripheral μ-opioid receptors. As a PEGylated derivative of naloxone, the ability of naloxegol to cross the blood brain barrier is limited. Naloxegol acts primarily on the gut μ-opioid receptors and counteracts opioid-induced

constipation (OIC) with limited impact on opioid-mediated analgesic effects on the central nervous system (CNS) at the intended therapeutic doses.

PEGylation reduced the passive permeability of naloxegol and renders it to be a substrate of P-glycoprotein which taken together suggest that CNS penetration of naloxegol is minimal.

In vitro studies demonstrate that naloxegol is a neutral antagonist of μ-opioid receptors (see Part II: DETAILED PHARMACOLOGY).

Dependence/tolerance: MOVANTIK is a peripherally acting μ-opioid receptor antagonist with no known risk of dependency.

Effect on cardiac electrophysiology: In a randomized, double-blind, placebo-controlled, 4-way cross-over thorough ECG study (including QTc prolongation) to assess the effect of a single therapeutic (25 mg) and supratherapeutic (150 mg) dose of naloxegol in healthy male subjects (N=51), naloxegol did not have an effect on QTcF (QTcF= $QT/RR^{0.33}$) interval at the 25 mg therapeutic dose. At the supratherapeutic dose of naloxegol 150 mg, the maximum mean difference from placebo in the QTcF interval was 3.1 ms (90% CI 1.3, 4.9) at 1.5 and 2 h post-dosing. Changes in heart rate, RR, PR, and QRS ECG intervals were similar between placebo and naloxegol 25 or 150 mg. The C_{max} of naloxegol was 37.7 ng/mL at the 25 mg dose and 291 ng/mL at the 150 mg dose.

Pharmacokinetics

Naloxegol demonstrates linear pharmacokinetics. Exposure to naloxegol is approximately dose proportional.

Table 3 Summary of main naloxegol pharmacokinetic parameters in healthy male and female volunteers

	C_{max} (ng/mL)	$t_{½}$ (h)	CL/F (L/hr)	Vz/F (L)
Single oral dose mean (25 mg)[a]	N=42	N=42	N=42	N=42
Geometric Mean	38.3	6.99	173	1740
SD	21.2	4.70	99.4	1360
range	(11.4 – 103)	(2.36 – 26.5)	(65.7 – 464)	(621 – 7790)

[a] Fasted state (commercial formulation)

Abbreviations: CL/F Apparent clearance of drug (total clearance of dose/fraction of dose systemically available). VzF Apparent volume of distribution during the terminal phase. $t_{1/2}$ Half-life. SD Standard Deviation

Absorption: Following oral administration, naloxegol is absorbed rapidly, with peak concentrations (C_{max}) achieved in less than 2 hours. In a majority of subjects, a secondary

plasma concentration peak of naloxegol was observed approximately 0.4 to 3 hours after the first peak.

Naloxegol as a crushed tablet mixed in water, given orally or administered through a nasogastric tube into the stomach demonstrated comparable bioavailability to the whole tablet administered orally with water. The median T_{max} was 0.75 and 1.50 hours (range 0.23 to 5.02 hours) for the crushed tablet given orally and the crushed tablet given via nasogastic tube, respectively.

Food Effects: A high-fat meal increased the extent and rate of naloxegol absorption. The C_{max} and AUC were increased by approximately 30% and 45%, respectively. MOVANTIK should be taken in the morning on an empty stomach, approximately 1 hour prior to the first meal of the day or 2 hours post-meal (see DOSAGE AND ADMINISTRATION, Dosing Considerations).

Distribution: The mean apparent volume of distribution during the terminal phase (Vz/F) in healthy volunteers ranged from 968 to 2140 L across dosing groups and studies. Plasma protein binding of naloxegol in humans was low and the fraction unbound ranged from 80% to 100%.

Metabolism: Naloxegol is mainly metabolized by the CYP3A4 enzyme system. In a mass balance study in humans, a total of 6 metabolites were identified in plasma, urine and feces. These metabolites represented more than 32% of the administered dose and were formed via N-dealkylation, O-demethylation, oxidation and partial loss of the PEG chain. None of the metabolites were present in >10% of the plasma concentrations of parent or drug related material.

Excretion: Following oral administration of radio-labelled naloxegol, 68% and 16% of total administered dose were recovered in the feces and urine, respectively. Parent naloxegol excreted in the urine accounted for less than 6% of the total administered dose. Thus renal excretion is a minor clearance pathway for naloxegol. In clinical pharmacology studies, the half-life of naloxegol at therapeutic dose ranged from 6 to 11 hours.

Special Populations and Conditions

Pediatrics (<18 years of age): The pharmacokinetics of naloxegol in the pediatric population has not been established and is not indicated in this patient population.

Geriatrics (≥65 years of age): There is a small effect of age on the pharmacokinetics of naloxegol (approximately 0.7% increase in AUC for every year increase in age). No dose adjustment for MOVANTIK is recommended for the elderly.

Elderly healthy Japanese subjects had naloxegol steady state plasma levels (AUC and C_{max}) that were approximately 50% greater than those obtained in young healthy subjects.

Gender: There is no gender effect on the pharmacokinetics of naloxegol.

Race: In African American subjects, there was an approximately 20% decrease in the AUC and 10% decrease in C_{max} of naloxegol when compared to Caucasian subjects. In Asian subjects, it was suggested that there was a 30% increase in C_{max} of naloxegol.

Renal impairment: As renal clearance is a minor route of elimination for naloxegol, regardless of severity (i.e., moderate, severe and end stage renal failure), the impact of renal impairment on the pharmacokinetics of naloxegol was minimal in most subjects. However, in 2 out of 8 patients (in both the moderate and severe renal impairment groups but not in the end stage renal failure group), up to 10-fold increases in the exposure of naloxegol were observed. Exposure of naloxegol in end-stage renal disease patients on hemodialysis was similar to healthy volunteers with normal renal function.

The starting dose for patients with moderate, severe, or end-stage renal impairment is 12.5 mg. The dose can be increased to 25 mg if the 12.5 mg dose is well tolerated. As a few patients may experience higher than normal exposure to naloxegol, treatment with MOVANTIK should be discontinued if side effects impacting tolerability occur (see DOSAGE AND ADMINISTRATION, Special Populations).

Hepatic impairment: Less than 20% decreases in AUC and 10% decreases in C_{max} were observed in patients with mild and moderate hepatic impairment (Child-Pugh Class A and B). The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of naloxegol was not evaluated, therefore, the use of MOVANTIK is not recommended in such patients (see WARNINGS AND PRECAUTIONS, Hepatic).

STORAGE AND STABILITY

Store at controlled room temperature (15-30°C).

Keep in a safe place out of the reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

MOVANTIK (naloxegol oxalate) 12.5 mg tablets are oval, biconvex, mauve, film-coated, intagliated with "12.5" on one side and "nGL" on the other side.

MOVANTIK 25 mg tablets are oval, biconvex, mauve, film-coated, intagliated with "25" on one side and "nGL" on the other side.

Composition

MOVANTIK 12.5 mg and 25 mg tablets contain the following non-medicinal ingredients:

Tablet core: mannitol, microcrystalline cellulose, croscarmellose sodium, propyl gallate, magnesium stearate

Tablet coat: hypromellose, titanium dioxide, macrogol 400, iron oxide red, iron oxide black

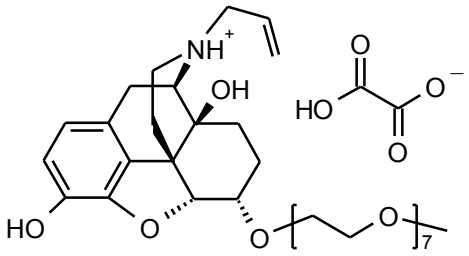
Packaging

Both strengths of MOVANTIK are available in high-density polyethylene (HDPE) bottles containing desiccant, with a white polypropylene child resistant screw cap. Each pack contains 30 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common Name:	naloxegol oxalate
Chemical Name:	(5α,6α)-17-allyl-6-(2,5,8,11,14,17,20-heptaoxadocosan-22-yloxy)-4,5-epoxymorphinan-3,14-diol oxalate
Molecular Formula:	$C_{34}H_{53}NO_{11}C_2H_2O_4$
Molecular Mass:	741.8 g/mol
Structural Formula:	
Physicochemical Properties:	Naloxegol oxalate is a white to off-white crystalline powder, and is highly soluble in aqueous media (with solubilities exceeding 50 mg/mL) over the pH range of 1 to 7.5. It exhibits two pKa values: 8.4 (amine) and 9.5 (phenol). The melting point of naloxegol oxalate is 92°C, and it has showed a minor uptake of moisture below 70% relative humidity and is not considered hygroscopic.

CLINICAL TRIALS

Treatment of Opioid-Induced Constipation (OIC)

Table 4 Summary of Pivotal Clinical Trials in OIC

Study No.	Trial design	Dosage, route of administration and duration	Study subjects per treatment arm (n=number)	Mean age (Range)	Gender M/F
KODIAC 4	DB, parallel group, placebo-controlled study with 2-week OIC confirmation and 12-week treatment	Oral once daily dosing of naloxegol 12.5 mg and 25 mg 12-week treatment phase	n=641[a] (213 for 12.5 mg; 214 for 25 mg and 214 placebo)	52.3 (18-83)	248/393[a]
KODIAC 5	DB, parallel group, placebo-controlled study with 2-week OIC confirmation and 12-week treatment	Oral once daily dosing of naloxegol 12.5 mg and 25 mg 12-week treatment phase	n=696[a] (232 for 12.5 mg; 232 for 25 mg and 232 placebo)	52.1 (19-82)	255/441[a]

a Patients included in the intent to treat (ITT) analysis set.

Abbreviations: DB Double-blind.

Efficacy Studies

The efficacy of MOVANTIK (naloxegol oxalate) in the treatment of OIC was assessed in two replicate, multicentre, randomized, double-blind, placebo-controlled studies of 12 weeks duration in patients with OIC and non-cancer related pain (see Table 4). Patients taking a minimum of 30 morphine equivalent units (meu) of opioids per day for at least 4 weeks before enrolment and self-reported OIC were eligible to participate. OIC was confirmed through a 2-week run-in period and defined as <3 spontaneous bowel movements (SBMs) per week on average with at least one or more symptoms of straining, hard/lumpy stools and or sensation of incomplete evacuation/anorectal obstruction in at least 25% of bowel movements. Patients with possible clinically important disruption of the blood-brain barrier were excluded. Patients who had a QTcF >500 msec at screening, a recent history of myocardial infarction within 6 months before randomization, symptomatic congestive heart failure, or had any other overt CV disease were also excluded from the clinical studies. In addition, patients with moderate or severe hepatic insufficiency were excluded.

Response to study drug over 12 weeks in patients who had an inadequate response to laxatives in the 2 weeks prior to enrolment was evaluated. The laxative response status was determined at the screening visit using an investigator administered questionnaire (Stool Symptom Screener) about previous laxative use and constipation symptoms over the past 2 weeks. Patients categorized as Laxative Inadequate Responder (LIR) reported to have used a minimum of one class of laxative at least 4 days over the 14 days preceding first study visit and either moderate, severe or very severe intensity of at least one of the following OIC symptoms: incomplete bowel movements, hard stools, straining or sensation of needing to pass a bowel movement but unable to do so.

Throughout the study, patients were prohibited from using laxatives other than bisacodyl rescue laxative if they had not had a bowel movement for 72 hours. An SBM was defined as a bowel movement without rescue laxative taken within the past 24 hours.

A total of 652 patients in KODIAC 4 and 700 patients in KODIAC 5 were randomized to receive 12.5 mg or 25 mg of MOVANTIK or placebo once daily for 12 weeks. The mean age of the subjects was 52 years, 62% were women, 79% were white and 11% were 65 years of age or older. The mean daily opioid morphine equivalent dose was 138 mg/day and patients had been taking opioids for an average of 3.6 years for the current episode of pain. Back pain and arthritis were the most common reasons for pain (57% and 10%, respectively). Laxative use within the 2 weeks prior to enrolment was reported by 71% of patients and by 84% percent within 6 months prior to enrolment. Patients were stratified based on their response to laxative use (LIR, Laxative Adequate Responders (LAR), and Laxative Unknown Responders (LUR)) and were to be randomly assigned to one of the 3 treatment groups in a 1:1:1 ratio. The randomization procedure was designed to ensure that a minimum of 50% of patients in were LIR.

The primary efficacy endpoint was the response over the 12-week treatment period, defined by ≥3 SBMs per week and a change from baseline of ≥1 SBM per week for at least 9 out of the 12 treatment weeks including 3 out of the last 4 treatment weeks. The first of three multiplicity protected secondary endpoints was the 12-week responder rate in the LIR subgroup.

Study results: Results across the confirmatory studies demonstrated durability and consistency of efficacy for MOVANTIK in the treatment for OIC. In both studies, 54% of the patients were categorized as LIR. LIR patients treated with MOVANTIK 25 mg demonstrated statistically significant higher rate of response, as compared to placebo in both studies. MOVANTIK 12.5 mg demonstrated a statistically significant difference in the response rate over placebo in KODIAC 4 only (see Table 5).

There was no definitive evidence for differential effects of age, gender, or weight on efficacy of MOVANTIK. The subjects who participated in KODIAC 4 and KODIAC 5 were taking a wide-range of opioids.

Table 5 Analysis of response rate (SBM) for Weeks 1 to 12 in the LIR population, KODIAC 4 and 5 (Intent-to-treat analysis set)

	KODIAC 4			KODIAC 5			Pooled		
	PLA	**NGL 12.5 mg**	**NGL 25 mg**	**PLA**	**NGL 12.5 mg**	**NGL 25 mg**	**PLA**	**NGL 12.5 mg**	**NGL 25 mg**
n	118	115	117	121	125	124	239	240	241
% responders (p-value)	28.8	42.6 (0.028*)	48.7 (0.002*)	31.4	42.4 (0.074)	46.8 (0.014*)	30.1	42.5 (0.005)	47.7 (<0.001)
Difference in responder rates (95%CI) NGL 25mg vs PLA		**19.9** (7.7, 32.1)			**15.4** (3.3, 27.4)			**17.6** (9.0, 26.2)	

* Statistical significant under Multiple Testing Procedure (MTP).

Abbreviations: h hour; ITT intent to treat; LIR Laxative Inadequate Responders; NGL Naloxegol; OIC Opioid-Induced Constipation; PLA Placebo; SBM Spontaneous Bowel Movement

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

A response analysis identical to the primary efficacy analysis except for using *complete* spontaneous bowel movement (CSBM) instead of SBM showed that in the pooled KODIAC 4 and 5 studies, the response rate was larger with MOVANTIK 25 mg (20.7%), as compared to placebo (9.6%), for a difference of 11.1% (p-value=0.001).

Among LIR patients on MOVANTIK 25 mg, approximately 54% (61% in KODIAC 4 and 48% in KODIAC 5) of patients had an SBM within 12 hours of the first dose.

Furthermore, results from secondary endpoints (mean SBM's per week, mean days per week with at least 1 SBM, mean degree of straining and mean stool consistency), generally supported the findings from the primary endpoint and the benefit of MOVANTIK for OIC in patients with non-cancer pain and who are inadequate responders to laxative(s).

There were no clinically relevant differences between MOVANTIK and placebo in average pain intensity or in clinically important changes in daily opioid dose over the 12 week studies.

DETAILED PHARMACOLOGY

Non-Clinical Pharmacology

Primary pharmacodynamics: The pharmacological profile of naloxegol was characterised in *in vitro* binding assays demonstrating that naloxegol binds to μ-, δ- and κ- opioid receptors, with highest affinity at μ-opioid receptors. In [^{35}S]GTPγS binding assays, naloxegol was shown to be a full and competitive antagonist at human μ-opioid receptors, with no significant agonist efficacy. In addition, *in vitro* binding data indicate that naloxegol also is an antagonist of δ-opioid receptors, and it is a weak κ-opioid receptor partial agonist. However, naloxegol

does not show any signs of κ-opioid agonism in a more physiological system (rabbit vas deference assay).

In *in vivo* studies naloxegol was shown to reverse morphine-induced slowing of gastrointestinal transit at doses lower than those that reverse morphine analgesia, providing evidence of a separation between desired peripheral gastrointestinal effect and undesired CNS morphine antagonism in rats.

Secondary pharmacodynamics: Naloxegol was tested in a diverse panel of 327 targets covering a broad spectrum of receptors, ion channels and enzymes. Significant activity was only seen at the to μ-, δ- and κ- opioid receptors.

Safety pharmacology: Naloxegol had no effects in assays for general behavioral effects, proconvulsive activity, analgesic activity and abuse potential, suggesting that naloxegol is unlikely to cause any CNS-mediated adverse events in man. These results also indicate a low likelihood of an opioid abuse liability. Naloxegol had an IC_{50} >300 μM at the hERG ion channel and was inactive against further 7 cardiac channels. Cardiovascular effects were seen in a dog telemetry study where naloxegol caused non dose-related transient decreases in both systolic and diastolic blood pressure, left ventricular systolic pressure and indexes of cardiac myocardial contractility and relaxation. Heart rate was also slightly increased. The No Observed Effect Level (NOEL) for the decreases in arterial blood pressure, left ventricular systolic pressure, and cardiac contractility and relaxation was 5 mg/kg, with maximum exposures comparable to the human exposure (C_{max}) at the recommended human dose (RHD) of 25 mg/day. The telemetry findings in the dog study are unlikely to be clinically relevant. No cardiovascular effects were observed on canine myocyte contractility at up to 100 μM or in a rat heart Langendorff preparation at up to 10 μM.

The lack of effect of naloxegol on cardiac ion channels and cardiac myocytes, as well as the absence of cardiovascular effects in repeat-dose toxicology studies, indicate that naloxegol is unlikely to have a direct effect on the heart or ECG parameters.

Rat plethysmography, gastric emptying/intestinal transport and renal function studies indicated that naloxegol is unlikely to have any adverse effect on the respiratory system, gastrointestinal or renal systems at the RHD.

Pharmacokinetics: Absorption, distribution, metabolism, and excretion (ADME) properties of naloxegol were investigated *in vitro* (in Caco-2 cells, hepatocytes and brain tissues) and *in vivo* (in mouse, rat, dog, non-human primate and human). Naloxegol is considered to be a low permeability molecule. The *in vitro* unbound fraction of naloxegol in plasma ranged from 47% to 100% across species. Brain perfusion studies demonstrated a slower rate of entry into the brain for naloxegol (4.1 pmol/g brain/sec), similar to the slow permeation reference atenolol (5.17 pmol/g brain/sec), compared to naloxone (60.2 pmol/g brain/sec). Low brain penetration potential was further confirmed in a rat quantitative whole-body autoradiography study. In rat, biliary excretion contributed substantially to the elimination of ^{14}C-naloxegol following a single oral administration. *In vitro*, naloxegol appears to be a substrate of cytochrome P450 3A (CYP3A) and P-glycoprotein, and appears to have low potential to

inhibit cytochrome P450 enzymes (CYPs). *In vitro* metabolism investigations using hepatocytes demonstrated the similarity in metabolic pathways across all species tested, and all metabolites observed in human hepatocytes have also been observed in animal hepatocytes.

TOXICOLOGY

Animal toxicology

Most of the effects observed in the pivotal repeat dose toxicity studies in the two main toxicology species, the rat and dog, and the mouse as a second rodent species for carcinogenicity assessment, were generally limited to effects on body weight and food consumption as well as stress-related findings which occurred at dose levels above the NOAEL and generally at doses at or close to the maximum tolerated dose level. Whilst most findings in the repeat dose toxicity studies were likely not to relate to inhibition of opioid receptor signaling, a dose-related finding of soft stool/diarrhea in the dog may reflect exaggerated pharmacological effects. Some findings, such as ataxia, tremors and hypoactive behaviour seen at high doses in the dog, were likely to be indicative of CNS exposure. The only target organ of toxicity identified across all main toxicity species was the liver (weight increase and hypertrophy in rats, weight increase in dogs), but these findings were slight, not adverse and reversible. Safety pharmacology endpoints were included in the repeat-dose toxicology studies, with cardiovascular endpoints assessed in all dog studies. There were no adverse effects observed on blood pressure and ECG parameters (including heart rate and QTcV, single time-point/registration occasion) in dogs at doses up to 200 mg/kg/day.

The NOAEL in the chronic rat (6-month) and dog (9-month) toxicity studies was 200 mg/kg/day with exposure multiples of at least 248x (rat) and 165x (dog) the human exposure at the RHD. Thus, findings in the repeat dose studies only occur at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Carcinogenesis

Carcinogenicity studies of naloxegol were conducted in Sprague-Dawley rats and CD-1 mice. In a 104-week study in CD-1 mice, naloxegol was not carcinogenic. Naloxegol was administered orally to rats at doses of 40, 120, and 400 mg/kg/day for at least 93 weeks. Naloxegol did not cause an increase in tumours in female rats. In male rats, a dose-related increase in Leydig cell adenomas and interstitial cell hyperplasia was observed at 120 mg/kg/day and above. A dose-related decrease in the incidence of pituitary adenomas was noted in male rats at 400 mg/kg/day and female rats at 120 mg/kg/day and above. A dose-related decrease in the incidence of mammary carcinomas in females was noted at 120 mg/kg/day and above. The no observed effect level for increased tumour incidence was 40 mg/kg/day in male and 400 mg/kg/day in female rats (51 (males) and 1030 (females) times the human exposure (AUC) at the RHD of 25 mg/day. The observed neoplastic changes are well known hormonal and centrally mediated effects in the rat which are not relevant for humans.

Mutagenesis

The genotoxic potential of naloxegol was evaluated in a battery of *in vitro* and *in vivo* test systems. Naloxegol did not show any mutagenic activity in a bacterial mutation (Ames) test. Naloxegol did not induce mutations in the mouse Lymphoma TK assay or chromosome damage in the *in vivo* mouse micronucleus test. The overall weight of evidence for naloxegol supports the conclusion that this compound is not genotoxic and does not represent a carcinogenic risk to man.

Reproduction and Development

Naloxegol was found to have no effect on fertility of male and female rats at oral doses up to 1000 mg/kg per day (greater than 1000 times the human therapeutic exposure (AUC) at the recommended human dose of 25 mg/day).
Naloxegol had no effect on fetal development at oral doses up to 750 mg/kg per day in rats (1452 times the human exposure (AUC) at the recommended human dose of 25 mg/day) and up to 150 mg/kg per day in rabbits (79 times the human exposure (AUC) at the recommended human dose of 25 mg/day). Naloxegol had no effects on parturition or postnatal development in rats at exposures equivalent to 225 times the human exposure (C_{max}) at the recommended human dose of 25 mg/day). The relevance of the observed developmental effects observed in the rat and rabbit to human safety is considered negligible since they occurred at maternal exposures that are clinically irrelevant.

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IMPORTANT: PLEASE READ

PART III:
CONSUMER INFORMATION

Pr MOVANTIK®

Naloxegol Tablets

This leaflet is part III of a three-part "Product Monograph" published when MOVANTIK was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about MOVANTIK. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

WHAT THE MEDICATION IS USED FOR:
MOVANTIK (naloxegol oxalate) is used to treat constipation that is specifically caused by pain medications, called opioids, taken on a regular basis. It is used in non-cancer pain patients when laxative(s) have not provided acceptable relief of constipation.

Constipation related to opioids can result in symptoms such as:

- stomach pain;
- rectal straining (having to push very hard to move the stool out, which can also cause pain in the anus during pushing);
- hard stools (stools which are hard "like a rock");
- incomplete emptying of the rectum (after having bowel movement, the feeling as if a stool is still in the rectum which needs to come out).

WHAT IT DOES:
Opioids can slow down the movement of the bowel and cause constipation. MOVANTIK is a peripherally acting opioid receptor antagonist. This means that MOVANTIK blocks the constipating effects of opioids in the bowel without affecting the pain relief provided by the opioid that you are taking. About one-half of patients can expect a bowel movement within 12 hours after taking MOVANTIK for the first time.

WHEN IT SHOULD NOT BE USED:
You should not take MOVANTIK if:

- You are allergic to naloxegol oxalate or other medications in this class or to any of the ingredients of MOVANTIK (see WHAT THE IMPORTANT NONMEDICINAL INGREDIENTS ARE).
- Your bowels are, or may be, blocked or you have been warned that your bowels are at risk of becoming blocked.
- You are taking certain other medications such as ketoconazole or voriconazole (to treat fungal infections), clarithromycin (an antibiotic) or ritonavir (for HIV).

WHAT THE MEDICINAL INGREDIENT IS:
Naloxegol (as naloxegol oxalate)

WHAT THE IMPORTANT NONMEDICINAL INGREDIENTS ARE:
MOVANTIK tablets contain the following non-medicinal ingredients: croscarmellose sodium, hypromellose, iron oxide black, iron oxide red, macrogol 400, magnesium stearate, mannitol, microcrystalline cellulose, propyl gallate, titanium dioxide.

WHAT DOSAGE FORMS IT COMES IN:
MOVANTIK comes in 12.5 mg and 25 mg tablet strengths. The 12.5 mg tablets are oval, biconvex, mauve, film-coated, engraved with "12.5" on one side and "nGL" on the other side. The 25 mg tablets are oval, biconvex, mauve, film-coated, engraved with "25" on one side and "nGL" on the other side.

WARNINGS AND PRECAUTIONS

BEFORE you use MOVANTIK, talk to your healthcare professional if:

- You have severe stomach ulcers, Crohn's Disease or diverticulitis (illness where your gut is inflamed), cancer in your gut or 'peritoneum' (the lining of your stomach area), or any condition that might damage the wall of your bowel.
- You currently have severe or persistent stomach pain and/or diarrhea.
- Your blood brain barrier has been damaged, such as after a recent brain injury, or if you have a disease of the central nervous system like multiple sclerosis or Alzheimer's Disease.
- You experience a lack of pain relief from your opioid medicine or symptoms of opioid withdrawal syndrome;
- You have kidney problems.
- You have severe liver problems (as MOVANTIK use is not recommended).
- You are taking methadone.
- You have had a heart attack within the last 6 months, have had heart failure or other severe problems with your heart.
- You are taking any other medications, including those obtained without a prescription, or natural health products (see INTERACTIONS WITH THIS MEDICATION).

If you are pregnant or planning to become pregnant, MOVANTIK use is not recommended.

If you are breastfeeding or planning to breastfeed, MOVANTIK use is not recommended. Taking MOVANTIK while you are breastfeeding may cause opioid withdrawal in your baby.

If your opioid medication is to be stopped for more than 24 hours while taking MOVANTIK you should talk to your doctor.

If you develop severe or persistent stomach pain and/or diarrhea you should stop taking MOVANTIK and tell your doctor immediately.

INTERACTIONS WITH THIS MEDICATION

Tell your healthcare professional if you are taking, or have recently taken, any other medications, including laxatives. This includes medications obtained without a prescription and herbal medications.

Tell your healthcare professional if you are taking the following medications or remedies that may interact with MOVANTIK:

- Certain medications such as ketoconazole or voriconazole (to treat fungal infections) clarithromycin (an antibiotic) or ritonavir (for HIV);
- Certain medications such as rifampin (an antibiotic), carbamazepine or phenytoin (for epilepsy);
- Certain medications such as diltiazem or verapamil (for high blood pressure or chest pain) or erythromycin (an antibiotic);
- Methadone;
- Herbal remedy St. John's wort (Hypericum perforatum);
- Grapefruit or grapefruit juice;
- Medications called "opioid antagonists" such as naltrexone and naloxone (used to counteract the effects of opioids).

Know all of the medications you take. Keep a list of them with you to show your healthcare professional.

PROPER USE OF THIS MEDICATION

MOVANTIK is not indicated for use in patients below 18 years of age, as it has not been studied in this age group.

MOVANTIK should be taken in the morning on an empty stomach at least 1 hour before the first meal of the day or 2 hours after. You should not consume grapefruit or grapefruit juice whilst taking MOVANTIK.

Tablets should be swallowed whole with water.

If you have trouble swallowing the tablet whole, you can crush it and mix with water in the following way:

- Crush the tablet to a powder.
- Pour the powder into half of a glass of room temperature non-carbonated water (120 mL or 4 oz).
- Stir and drink immediately.
- To make sure there is no medicine left, rinse the empty glass with another half glass of room temperature non-carbonated water (120 mL or 4 oz) and drink it.

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

1. Flush the NG tube with 1 ounce (30mL) of water using a 60 mL syringe.
2. Crush the tablet to a powder in a container and mix with approximately 2 ounces (60mL) of water.
3. Draw up the mixture using the 60 mL syringe and administer the syringe contents through the NG tube.
4. Add approximately 2 ounces (60mL) of water to the same container used to prepare the 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.

You could have a bowel movement within 12 hours after taking your first dose of MOVANTIK.

USUAL DOSE:
Always take this medication exactly as your healthcare professional had told you. Check with your healthcare professional if you are not sure.

Adults: The recommended dose is 25 mg orally once daily.

When you start taking MOVANTIK, stop using all other laxatives. You can start your laxatives again once your doctor tells you to.
OVERDOSE:

In case of drug overdose, contact a healthcare practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

MISSED DOSE:
What you should do if you forget to take a tablet depends on the length of time until your next dose.

- If it is 12 hours or more until your next dose: Take the missed tablet as soon as you remember. Then, take the next dose as normal.
- If it is less than 12 hours until your next dose: Skip the missed dose. Then, take the next dose at the normal time.

Do not take a double dose (two doses at the same time) to make up for a forgotten tablet.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medications MOVANTIK can cause side effects, although not everybody gets them.

The following side effects may happen with MOVANTIK:

- Very common (may affect more than 1 in 10 patients): stomach pain, diarrhea (passing of frequent, watery stools).

- Common (may affect more than 1 in 100 but less than 1 in 10 patients): passing wind, nausea, vomiting, runny or stuffy nose, headache, excessive sweating.

- Uncommon (may affect up to 1 in 100 people): opioid withdrawal symptoms (may include nausea, vomiting, diarrhea, excess sweating, muscle aches, increased tearing, insomnia, yawning, goosebumps, runny nose, dilation of the pupil, feeling depressed, fever).

- Not known: hypersensitivity, gastrointestinal perforation.

Stop taking MOVANTIK and tell your doctor immediately if:

- You have **severe** or **persistent** stomach pain, as cases of gastrointestinal perforation (a hole in your intestine or stomach) have occurred.

  or

- You have **severe** diarrhea (watery, bloody or persistent).

Other side effects may occur when using MOVANTIK.

If any of the side effects persist or worsen, or if you notice any side effects not listed in this leaflet, contact your healthcare professional.

HOW TO STORE IT

MOVANTIK should be kept out of the reach and sight of children.

Store your MOVANTIK tablets at room temperature (15-30°C).

The expiry date of this medication is printed on the package label. Do not use the medication after this date.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect.
- Call toll-free at 1-866-234-2345.
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 1908C
    Ottawa, Ontario
    K1A 0K9

  Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

NOTE: This INFORMATION FOR THE CONSUMER leaflet provides you with the most current information at the time of printing.

The most current information, the Consumer Information Leaflet plus the full Product Monograph, prepared for health professionals can be found at the Health Canada website (http://hc-sc.gc.ca/index-eng.php);

or by contacting the sponsor, Knight Therapeutics Inc. at medinfo@gudknight.com, or by calling 1-844-483-5636.

This leaflet was prepared by:
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