MOVANTIK™

naloxegol (as oxalate)

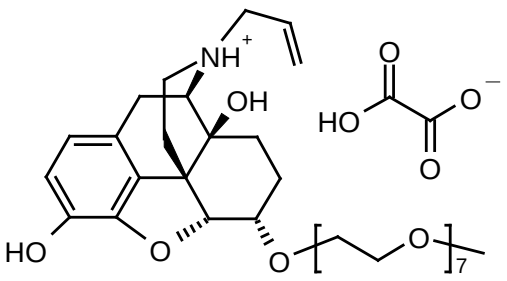
PRODUCT INFORMATION

NAME OF THE MEDICINE

The active ingredient in MOVANTIK is naloxegol (as oxalate), a peripherally acting μ-opioid receptor antagonist (PAMORA).

The chemical name for naloxegol oxalate is: (5α,6α)-17-allyl-6-(2,5,8,11,14,17,20-heptaoxadocosan-22-yloxy)-4,5-epoxymorphinan-3,14-diol oxalate

The chemical structure of naloxegol oxalate is:



CAS number: 1354744-91-4
Molecular formula: $C_{34}H_{53}NO_{11}C_2H_2O_4$
Molecular weight: 741.8

DESCRIPTION

Each film-coated tablet contains naloxegol 12.5 mg or 25 mg (as naloxegol oxalate 14.2 mg or 28.5 mg) and the following inactive ingredients: mannitol, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, propyl gallate, hypromellose, titanium dioxide, macrogol 400, iron oxide red and iron oxide black.

PHARMACOLOGY

Pharmacological actions

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, increased absorption of fluid from intestines and increased sphincter tone, which may cause constipation in 40-90% of individuals who take opioids.

Naloxegol is a PEGylated derivative of the μ-opioid receptor antagonist naloxone. *In vitro* studies demonstrate that naloxegol is a neutral antagonist of μ-opioid receptors, a neutral antagonist of δ-opioid receptors and a weak partial agonist at the κ-opioid receptors, with the highest binding affinity at μ-opioid receptors. The partial agonism on κ-opioid receptors was further explored in a more physiological system the rabbit *vas deferens* assay, and naloxegol was shown to have no agonist activity in this assay.

PEGylation reduces naloxegol's passive permeability and also renders the compound a substrate for the P-glycoprotein transporter (P-gp). This ABC efflux transporter is highly expressed at the luminal (apical) membrane of brain capillary endothelial cells and serves as a defence mechanism to limit penetration and accumulation of naturally occurring toxins, xenobiotics, and drugs into the brain. Due to poorer permeability and increased efflux of naloxegol across the blood brain barrier, related to P-gp substrate properties, the CNS penetration of naloxegol is minimal.

Pharmacokinetics

Absorption

Following oral administration, naloxegol is absorbed rapidly, with peak concentrations (C_{max}) achieved at 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. Enterohepatic recirculation may be a possible explanation as extensive biliary excretion was seen in the rat. Across the range of doses evaluated peak plasma concentration and area under the plasma concentration-time curve (AUC) increase in a dose-proportional or almost dose proportional manner.

Food Effects

A high-fat meal increased the extent and rate of naloxegol absorption. After administration of a single tablet containing naloxegol 25 mg, the C_{max} and AUC were increased by approximately 30% and 45%, respectively.

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. Results from a QWBA (Quantitative Whole Body Autoradiography) study in the rat and the lack of antagonism of CNS opiate effect in humans at naloxegol doses less than 250 mg indicate minimal distribution of naloxegol into the CNS. Plasma protein binding of naloxegol in humans was low and the fraction unbound ranged from 80% to 100%.

Metabolism

In a mass balance study in humans, a total of 6 metabolites were identified in plasma, urine and faeces. These metabolites represented more than 32% of the administered dose and were formed via *N*-dealkylation, *O*-demethylation and partial loss of the PEG group followed by oxidation. 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 faeces 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 - 11 hours.

Special populations

Age and gender

Patients over 65 years (10.9%) of age have been well represented in the Phase III studies. There is a small effect of age on the pharmacokinetics of naloxegol (approximately 0.7% increase in AUC for every year increase in the age range evaluated in the clinical studies [18 to 78 years of age]). Clinical studies of MOVANTIK did not include sufficient numbers of patients aged 75 years or over (1.8%) to determine whether they respond differently than younger patients; however, the magnitude of this change is unlikely to be clinically meaningful. No dose adjustment is recommended for elderly patients.

There is no gender effect on the pharmacokinetics of naloxegol.

Race

The effect of race on the pharmacokinetics of naloxegol is small (approximately 20% decrease in the AUC of naloxegol when other groups are compared to Caucasian). Therefore, no dose adjustment is necessary.

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. In these patients renal impairment may adversely affect other clearance pathways (hepatic/gut drug metabolism, etc.) resulting in higher exposure. The starting dose for patients with moderate or severe renal impairment is 12.5 mg. If side effects impacting tolerability occur, naloxegol should be discontinued (see **DOSAGE AND ADMINISTRATION**). Exposure of naloxegol in ESRD patients on haemodialysis was similar to healthy volunteers with normal renal function.

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). Effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of nalogexol was not evaluated.

Paediatric population

The pharmacokinetics of naloxegol in the paediatric population has not been studied.

CLINICAL TRIALS

Clinical efficacy and safety

The efficacy of MOVANTIK was established in two replicate double-blinded, placebo-controlled studies of 12 weeks duration in patients with opioid-induced constipation (OIC) and non-cancer related pain (Studies 04 and 05). Patients taking opioid doses equivalent to between 30 and 1000 mg oral morphine daily for at least 4 weeks before enrolment and self-reported OIC were eligible to participate. OIC was confirmed through a two week run in period and defined as <3 spontaneous bowel movements (SBMs) per week on average with the accompanying constipation symptoms of straining, hard stools and incomplete evacuation associated with at least 25% of bowel movements. 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.

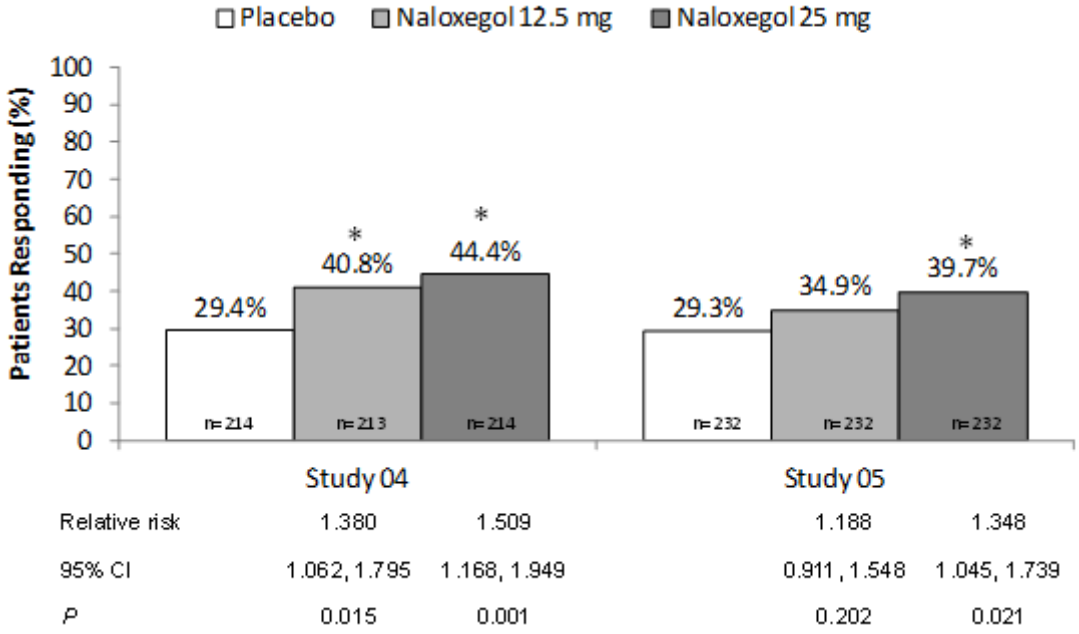
A total of 652 patients in Study 04 and 700 patients in Study 05 were randomised in a 1:1:1 ratio to receive 12.5 mg or 25 mg of MOVANTIK or placebo once daily for 12 weeks. The mean age of the subjects in these two studies was 52 years, 62% were women, 79% were white and 11% were 65 years of age or older. The mean daily opioid morphine equivalent dose was 138 mg per day and patients had been taking opioids for an average of 3.6 years for the current episode of pain. Back pain was the most common reason for pain (57%). Laxative use within the two weeks prior to enrolment was reported by 71% of patients and by 84% percent within 6 months prior to enrolment.

Primary end-point: Response to study drug in Studies 04 and 05

Efficacy and durability of effect were measured in the primary end-point as response over the 12-week treatment period to the study drug as defined by $\geq$3 SBMs per week and a change from baseline of $\geq$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 dose versus placebo for the primary end-point in Studies 04 and 05. Statistical significance for the 12.5 mg treatment group versus placebo was observed in Study 04 but not in Study 05. The response rates are provided in Figure 1 below.

Figure 1 Response rate for weeks 1 - 12 in Studies 04 and 05 (Intent-to-treat analysis set)



* Significance versus placebo, determined using the multiple testing procedure.
Analysis via Cochran Mantel-Haenszel test stratified by response to laxatives at baseline.

There was no definitive evidence for differential effects of age, gender, or weight on efficacy of MOVANTIK. The subjects who participated in Studies 04 and 05 were taking a wide-range of opioids. Treatment effect was consistent across opioid doses. There was no clinically relevant difference in efficacy of MOVANTIK between Caucasian and Black subjects. No meaningful subgroup analysis could be conducted for other races.

In the pooled data from Studies 04 and 05, responder rates were 29.4% for placebo, 37.8% for the 12.5 mg dose, and 41.9% for the 25 mg dose, with the relative risk (95% CI) for treatment effect versus placebo of 1.280 (1.063, 1.543) and 1.425 (1.190, 1.707) for the 12.5 mg and 25 mg groups respectively.

While OIC signs and symptoms improved in both the placebo and active treatment groups over the course of the studies, an additional 10 to 15% of patients given 25 mg MOVANTIK experienced a clinical response compared with those given placebo. In these studies 54% of patients were considered to have a history of inadequate response to laxatives. The response rate in these patients was similar to the overall response rate.

Key secondary end-points in Studies 04 and 05

There were three key secondary end-points which were controlled for multiple comparisons.

Response in the Laxative Inadequate Responders (LIR) subgroup

In Studies 04 and 05, 54% of the subjects were categorised as LIR. In Study 04, the response rates in the placebo, 12.5 mg and 25 mg dose LIR sub-groups were 28.8%, 42.6% and 48.7%, respectively. In study 05, the corresponding response rates were 31.4%, 42.4% and 46.8%, respectively. The improvement in response rates for 25 mg were statistically significant as compared to placebo in Studies 04 and 05, (p=0.002, p=0.014, respectively). The improvement in response rate for 12.5 mg was statistically significant compared to placebo in Study 04 (p=0.028) but not in Study 05.

Time to first post dose Spontaneous Bowel Movement (SBM)

In patients given 25 mg MOVANTIK daily the median time to first post-dose SBM was 5.9 h in Study 04 and 12.0 h in Study 05 compared with 35.8 h and 37.2 h for the placebo groups in these studies.

Mean days per week with at least 1 SBM

There was a statistically significant increase in the mean number of days per week with at least one SBM for the 25 mg dose in Studies 04 and 05 (mean increase of 0.8 and 0.7 days per week w/SBM). In Study 04 there was a statistically significant increase in the 12.5 mg dose (mean increase of 0.6 days per week/SBM).

Other pre-specified secondary endpoints

The 25 mg dose resulted in improved symptom of rectal straining scores (Study 04 p=0.008, Study 05 p<0.001) and stool consistency in Studies 04 and 05 versus placebo (Study 04 p=0.042, Study 05 p<0.001). The 25 mg dose increased percent days per week with at least 1 complete SBM in both studies (Study 04 p<0.001, Study 05 p<0.001).

MOVANTIK 25 mg dose resulted in a greater improvement (change from baseline) of patient assessment of constipation symptoms (PAC-SYM) total scores compared with placebo in one of the two studies at 12 weeks (Study 05, p=0.011) with a trend in improvement observed in the other study (Study 04, p=0.089). MOVANTIK 25 mg dose, compared with placebo, also resulted in greater improvement (change from baseline) of week 12 PAC-SYM rectal domain scores in both studies (p=0.003 and p<0.001, Studies 04 and 05, respectively) and for the stool domain scores in Study 05 (p<0.001), with a trend observed in Study 04 (p=0.072).

A “symptom responder” was defined as meeting both the 12-week responder criteria and demonstrating improvement in pre-specified OIC symptoms and no deterioration in symptoms. MOVANTIK 25 mg dose increased the symptom responder rates in both studies as compared to placebo (Study 04 p=0.003, Study 05 p=0.006). The symptom responder rates for placebo, 12.5 mg and 25 mg arms were 25.2%, 33.3% and 38.8% in Study 04 and 22.8%, 28.0% and 34.5% in Study 05.

Response to study drug over 12 weeks was tested in the subgroup of 2XLIR. In a pooled analysis of Studies 04 and 05, higher response rate in the 2XLIR population was observed for the 25 mg dose group compared with placebo (p=0.040). The responder rates in the 2XLIR population were placebo 30.0%, 12.5 mg 44.3% and 25 mg 44.4%.

There were no clinically relevant differences between MOVANTIK 12.5 mg, 25 mg, and placebo in average pain intensity, daily opioid dose or in opioid withdrawal scores over the 12-week study.

INDICATIONS

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

CONTRAINDICATIONS

MOVANTIK is contraindicated in patients with known or suspected gastrointestinal obstruction or in patients at increased risk of recurrent obstruction, due to the potential for gastrointestinal perforation (see **PRECAUTIONS**).

Patients with underlying cancer who are at heightened risk of gastrointestinal perforation, such as those with:

- underlying malignancies of gastrointestinal tract or peritoneum
- recurrent or advanced ovarian cancer
- vascular endothelial growth factor (VEGF) inhibitor treatment

MOVANTIK is contraindicated for use by any patient with a known serious hypersensitivity to this product, including its excipients, or any other opioid antagonist.

Concomitant use with dual P-gp/strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, ritonavir) or strong CYP3A4 inhibitors (e.g. voriconazole, grapefruit or grapefruit juice) can significantly increase exposure to naloxegol and is contraindicated (see **INTERACTIONS WITH OTHER MEDICINES**).

PRECAUTIONS

Potential for gastrointestinal perforation

Cases of gastrointestinal perforation have been reported in the post-marketed use of peripherally acting mu-opioid receptor antagonists (PAMORAs) in patients with advanced medical illness. 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 are advised to discontinue therapy with MOVANTIK and promptly notify their physician if they develop unusually severe or persistent abdominal pain.

Clinically important disruptions of the blood-brain barrier

MOVANTIK is a PAMORA with restricted access to the central nervous system (CNS). Patients with clinically important disruptions to the blood-brain barrier (e.g. primary brain malignancies, CNS metastases or other inflammatory conditions, active multiple sclerosis, recent brain injury, advanced Alzheimer's disease) were not included in clinical studies and may be at risk for naloxegol entry into the CNS. MOVANTIK should be prescribed with caution in such patients taking into account their individual benefit-risk balance with observation for potential CNS effects, such as symptoms of opioid withdrawal or reversal of analgesia. If evidence for opioid-mediated interference with analgesia or opioid withdrawal syndrome occurs, patients should be instructed to discontinue MOVANTIK and contact their physician.

Concurrent methadone use

Patients receiving methadone as primary therapy for their pain condition were observed in clinical trials to have a higher frequency of gastrointestinal adverse events (such as abdominal pain and diarrhoea) than patients not receiving methadone and, in a few cases, symptoms suggestive of opioid withdrawal when receiving MOVANTIK 25 mg were observed. This was observed in a higher proportion of patients taking methadone than those not taking methadone. Patients taking methadone for treatment of opioid addiction were not included in the clinical development programme and use of MOVANTIK in these patients should be approached with caution.

Gastrointestinal adverse reactions

Reports of severe abdominal pain and diarrhoea have been observed in clinical trials with the 25 mg dose, typically occurring shortly after initiation of treatment. There was a higher incidence of discontinuations in patients taking the 25 mg dose compared to placebo due to diarrhoea (0.7% for placebo versus 3.1% for MOVANTIK 25 mg) and abdominal pain (0.2% versus 2.9%, respectively). Patients should be advised to promptly report severe, persistent, or worsening symptoms to their physician. Consideration may be given to lowering the dose to 12.5 mg in patients experiencing severe gastrointestinal adverse events depending upon the response and tolerability of individual patients.

Opioid withdrawal syndrome

Cases of opioid withdrawal syndrome have been reported in the MOVANTIK clinical programme (DSM-5). Opioid withdrawal syndrome is a cluster of three or more of the following signs or symptoms: dysphoric mood, nausea or vomiting, muscle aches, lacrimation or rhinorrhoea, pupillary dilation or piloerection or sweating, diarrhoea, yawning, fever or insomnia. Opioid withdrawal syndrome typically develops within minutes to several days following administration of an opioid antagonist. If opioid withdrawal syndrome is suspected the patient should discontinue MOVANTIK and contact their physician.

Patients with CV conditions

MOVANTIK was not studied in the clinical trial programme in patients who had a recent history of myocardial infarction within 6 months, symptomatic congestive heart failure, overt cardiovascular (CV) disease or patients with a QT interval of ≥500 msec. MOVANTIK should be used with caution in these patients. A QTc study performed with MOVANTIK in healthy volunteers did not indicate any prolongation of the QT interval.

CYP3A4 inducers

MOVANTIK should be avoided in patients who are taking strong CYP3A4 inducers (e.g. carbamazepine, rifampicin, St. John's wort) (see **INTERACTIONS WITH OTHER MEDICINES**).

For information regarding concomitant use with CYP3A4 inhibitors, see **CONTRAINDICATIONS**, **INTERACTIONS WITH OTHER MEDICINES** and **DOSAGE AND ADMINISTRATION**.

Renal impairment

The dose for patients with moderate or severe renal impairment is 12.5 mg. If side effects impacting tolerability occur, MOVANTIK should be discontinued (see **Pharmacokinetics**).

Severe hepatic impairment

MOVANTIK has not been studied in patients with severe hepatic impairment. The use of MOVANTIK is not recommended in such patients.

Cancer-related pain

The safety and efficacy of MOVANTIK have not been assessed in patients with cancer-related pain. Therefore caution should be used when prescribing MOVANTIK to such patients.

Effects on fertility

Naloxegol had no effect on fertility in animals. 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 times the human exposure (AUC) at the recommended human dose of 25 mg/day).

Use in pregnancy – Category B1

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

Animal studies do not indicate harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development at exposures in excess of 70 times the human therapeutic exposure.

Because the blood brain barrier in humans is not fully developed until at least 6 months of age post partum, there is a theoretical potential for provoking opioid withdrawal in the foetus with use of an opioid receptor antagonist in the mother, who is concurrently using an opioid. Therefore, the use of MOVANTIK during pregnancy is not recommended.

Use in lactation

It is unknown whether naloxegol is excreted in human breast milk. Studies using suckling rats have shown that naloxegol is excreted in rat milk.

At therapeutic doses, most opioids (e.g. morphine, pethidine, methadone) are excreted into breast milk in minimal amounts. Given the immaturity of the blood brain barrier in neonates, there is a theoretical possibility that naloxegol could provoke opioid withdrawal in a breast-fed neonate whose mother is taking an opioid receptor agonist. Therefore, use in nursing mothers of infants <6 months old is not recommended. For nursing mothers of infants >6 months of age, a decision on whether to continue/discontinue breast feeding or to continue/discontinue use of MOVANTIK should be made taking into account the benefit of breast feeding to the child and the benefit of MOVANTIK to the woman.

Paediatric use

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

Use in elderly

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 is recommended for the elderly as this age group has been well represented in the phase III trials.

Carcinogenicity

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 tumors 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 recommended human dose of 25 mg/day (RHD)].

The observed neoplastic changes are well known hormonal and centrally mediated effects in the rat which are not relevant for humans.

Genotoxicity

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.

Use with laxatives

The safety and efficacy of MOVANTIK in combination with laxatives have not been assessed.

INTERACTIONS WITH OTHER MEDICINES

Given its mode of action as a peripherally acting mu-opioid receptor antagonist (PAMORA), naloxegol should not be co-administered with any other opioid antagonists.

Based on its *in vitro* enzyme and transporter induction and inhibition profile, naloxegol is not likely to perpetrate a pharmacokinetic (PK) based drug-drug interaction.

Naloxegol is a sensitive substrate of the CYP3A4 enzyme and a substrate of the P-gp transporter. Co-administration of dual P-gp/strong or moderate CYP3A4 inhibitors, or strong CYP3A4 inhibitors significantly increases naloxegol plasma concentrations (see **Pharmacokinetics**). Conversely, co-administration of a strong CYP3A4 inducer results in decreased plasma concentration.

Because naloxegol is highly soluble across the physiologic pH range and absorbed quickly following oral administration, its PK profile is unlikely to be affected by drugs that slow down GI motility or increase gastric pH.

Interaction with strong CYP3A4 inhibitors

Co-administration of ketoconazole and naloxegol resulted in a 12.9-fold (90% CI: 11.3-14.6) increase in naloxegol AUC and a 9.6-fold increase in naloxegol C_{max} (90% CI: 8.1-11.3), compared to when naloxegol was administered alone. Therefore, concomitant use with strong CYP3A4 inhibitors is contraindicated (see **CONTRAINDICATIONS**). Grapefruit and grapefruit juice have been classified as potent CYP3A4 inhibitors. No data are available on the concomitant use of naloxegol with grapefruit or grapefruit juice. Concomitant consumption of grapefruit or grapefruit juice while taking naloxegol is contraindicated.

Interaction with moderate CYP3A4 inhibitors

Co-administration of diltiazem and naloxegol resulted in a 3.4-fold (90% CI: 3.2-3.7) increase in naloxegol AUC and a 2.9-fold increase in naloxegol C_{max} (90% CI: 2.6-3.1), compared to when naloxegol was administered alone. Therefore, a dose adjustment of naloxegol is

recommended when co-administered with diltiazem and other moderate CYP3A4 inhibitors (see **DOSAGE AND ADMINISTRATION**). No dosage adjustment is required for patients taking weak CYP3A4 inhibitors.

Interaction with strong CYP3A4 inducers

Co-administration of rifampicin and naloxegol resulted in a 89% (90% CI: 88%-90%) decrease in naloxegol AUC and a 76% decrease in naloxegol C_{max} (90% CI: 69%-80%), compared to when naloxegol was administered alone. Therefore, naloxegol should be avoided in patients who are taking strong CYP3A4 inducers (see **PRECAUTIONS**).

Interaction with P-gp inhibitors

Co-administration of the P-gp inhibitor quinidine resulted in a 1.4 fold increase in the AUC (90% CI: 1.3-1.5) and a 2.4 fold increase in the C_{max} (90% CI: 2.2-2.8) of naloxegol. Co-administration of naloxegol and quinidine did not antagonise the morphine-induced miosis effect, suggesting that P-gp inhibition does not meaningfully change the capacity of naloxegol to cross the blood-brain barrier at therapeutic doses.

As the effects of P-gp inhibitors on the PK of naloxegol were small relative to the effects CYP3A4 inhibitors, the dosing recommendations for naloxegol when co-administered with medicinal products causing both P-gp and CYP3A4 inhibition should be based on CYP3A4 inhibitor status - strong, moderate or weak (see **CONTRAINDICATIONS**, **INTERACTIONS WITH OTHER MEDICINES** and **DOSAGE AND ADMINISTRATION**).

Laxatives

The safety and efficacy of MOVANTIK in combination with laxatives has not been assessed.

ADVERSE EFFECTS

Clinical study experience

MOVANTIK at doses up to 25 mg once daily was generally safe and well tolerated in patients with OIC in studies up to 52 weeks of treatment.

The most commonly reported Adverse Drug Reactions (ADRs) with MOVANTIK (≥5%) are: abdominal pain, diarrhoea, nausea, headache and flatulence.

Table 1 lists the adverse events that have been identified in the pivotal clinical studies with MOVANTIK:

Table 1 Adverse events (regardless of causality) occurring in ≥2% of OIC patients[a] with non-cancer pain[b] (Study 04 and Study 05 - Pooled 12 weeks duration)

Body System Preferred term	Placebo (N=444)	MOVANTIK 12.5 mg (N=441)	MOVANTIK 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			
Upper respiratory tract infection	12 (2.7)	9 (2.0)	11 (2.5)
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%).

DOSAGE AND ADMINISTRATION

The recommended dose of MOVANTIK is 25 mg once daily taken in the morning on an empty stomach.

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

Special populations

Paediatric use

Safety and efficacy of MOVANTIK have not been established in paediatric patients.

Use in the elderly

No dose adjustment is recommended for the elderly (see **Pharmacokinetics**).

Dosage in patients with renal impairment

The starting dose for patients with moderate or severe renal impairment is 12.5 mg. If side effects impacting tolerability occur, MOVANTIK should be discontinued. The dose can be increased to 25 mg if 12.5 mg is well tolerated by the patient (see **Pharmacokinetics**). No dosage adjustment is required for patients with mild renal impairment.

Dosage in patients with hepatic impairment

No dose adjustment is required for patients with mild to moderate hepatic impairment. Safety and efficacy have not been established in patients with severe hepatic impairment (see **Pharmacokinetics**).

CYP3A4 and P-gp inhibitors

Concomitant use with dual/P-gp strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, ritonavir) or strong CYP3A4 inhibitors (e.g. voriconazole) can significantly increase exposure to naloxegol and is contraindicated (see **CONTRAINDICATIONS**).

The starting dose of MOVANTIK should be 12.5 mg daily when co-administered with dual P-gp/moderate CYP3A4 inhibitors (e.g. diltiazem, verapamil, erythromycin) (see **INTERACTIONS WITH OTHER MEDICINES**). The dose can be increased to 25 mg if 12.5 mg is well tolerated by the patient.

No dose adjustment is necessary for dual P-gp/weak CYP3A4 inhibitors (e.g. quinidine, lapatinib, felodipine) or weak CYP3A4 inhibitors (e.g. cimetidine) (see **INTERACTIONS WITH OTHER MEDICINES**).

OVERDOSAGE

Doses of MOVANTIK up to 1000 mg were administered in healthy volunteers in clinical studies and were generally well tolerated, although a potential CNS effect (reversal of opioid-induced miosis, as measured by pupillometry) was observed in 1 volunteer in the 250 mg group and 1 volunteer in the 1000 mg group. In a clinical study of patients with OIC, a daily dose of 50 mg was associated with an increased incidence of intolerable gastrointestinal effects (primarily abdominal pain).

No antidote is known for MOVANTIK and 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.

Contact the Poisons Information Centre on 13 11 26 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

MOVANTIK 12.5 mg and 25 mg tablets are mauve, biconvex, oval, film-coated tablets in aluminium/aluminium blisters in pack sizes of 10 (sample pack) and 30 tablets.

Tablets are engraved with “nGL” on one side and the strength of the tablet on the other.

The tablets should be stored below 25°C.

NAME AND ADDRESS OF THE SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road
NORTH RYDE NSW 2113

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

7 January 2016

DATE OF MOST RECENT AMENDMENT

N/A