ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Moventig 12.5 mg film-coated tablets

Moventig 25 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Moventig 12.5 mg film-coated tablets
Each film-coated tablet contains naloxegol oxalate equivalent to 12.5 mg naloxegol.

Moventig 25 mg film-coated tablets
Each film-coated tablet contains naloxegol oxalate equivalent to 25 mg naloxegol.

Excipients with known effect
Each 12.5 mg tablet contains 0.9 mg sodium.
Each 25 mg tablet contains 1.9 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Moventig 12.5 mg film-coated tablet (tablet).
Oval, 10.5x5.5 mm, mauve tablet.

Moventig 25 mg film-coated tablet (tablet).
Oval, 13x7 mm, mauve tablet.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

For definition of inadequate response to laxative(s), see section 5.1.

4.2 Posology and method of administration

Posology
The recommended dose of Moventig is 25 mg once daily.

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

Special populations
Elderly
No dose adjustment is recommended based on age (see section 5.2).

Renal impairment
The starting dose for patients with moderate or severe renal insufficiency is 12.5 mg. If side effects impacting tolerability occur, naloxegol should be discontinued. The dose can be increased to 25 mg if 12.5 mg is well tolerated by the patient (see section 5.2). No dosage adjustment is required for patients with mild renal impairment.

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 section 5.2). Use in patients with severe hepatic impairment is not recommended.

CYP3A4 inhibitors
The starting dose for patients taking moderate CYP3A4 inhibitors (e.g. diltiazem, verapamil) is 12.5 mg once daily. The dose can be increased to 25 mg if 12.5 mg is well tolerated by the patient (see section 4.5).

No dose adjustment is required for patients taking weak CYP3A4 inhibitors (e.g. alprazolam, atorvastatin (see section 4.5).

Patients with cancer-related pain
No dose adjustment is required for patients with cancer-related pain (see sections 4.3 and 4.4).

Paediatric population
The safety and efficacy of naloxegol in children <18 years of age has not yet been established.

Method of administration
Oral use.

It is recommended that Moventig is taken in the morning, for patient convenience to avoid bowel movements in the middle of the night.

Moventig should be taken on an empty stomach at least 30 minutes prior to the first meal of the day or 2 hours after the first meal of the day.

For patients who are unable to swallow the tablet whole, the Moventig tablet can be crushed to a powder and mixed in half a glass of water (120 ml) and drunk immediately. The glass should be rinsed with a further half glass of water (120 ml) and the contents drunk. The mixture can also be administered via a nasogastric tube (CH8 or greater). It is important to flush the nasogastric tube through with water after administration of the mixture.

4.3 Contraindications

Hypersensitivity
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or any other opioid antagonist.

Gastrointestinal obstruction
Patients with known or suspected gastrointestinal (GI) obstruction or in patients at increased risk of recurrent obstruction, due to the potential for gastrointestinal perforation (see section 4.4).

Conditions in patients with cancer pain
- Patients with underlying cancer who are at heightened risk of GI perforation, such as those with:

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

Strong CYP3A4 inhibitors
Concomitant use with strong CYP3A4 inhibitors (e.g. clarithromycin, ketoconazole, itraconazole or telithromycin; protease inhibitors such as ritonavir, indinavir or saquinavir; grapefruit juice when consumed in large quantities), see section 4.5.

4.4 Special warnings and precautions for use

Conditions with increased potential for gastrointestinal perforation
Rare cases of gastrointestinal perforation have been reported in the post-marketed use of peripherally acting mu-opioid receptor antagonists in patients with advanced medical illness. Caution with regards to the use of naloxegol 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). The overall benefit-risk profile for each patient should be taken into account. Patients are advised to discontinue therapy with naloxegol and promptly notify their physician if they develop unusually severe or persistent abdominal pain.

Clinically important disruptions of the blood-brain barrier
Naloxegol is a peripherally acting mu-opioid receptor antagonist with restricted access to the central nervous system (CNS). The blood brain barrier integrity is important for minimizing naloxegol uptake into the 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, advanced Alzheimer's disease etc.) were not included in clinical studies and may be at risk for naloxegol entry into the CNS. Naloxegol 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 and/or interference with opioid-mediated analgesia. If evidence for opioid-mediated interference with analgesia or opioid withdrawal syndrome occurs, patients should be instructed to discontinue Moventig and contact their physician.

Concurrent methadone use
Patients taking methadone as primary therapy for their pain condition were observed in clinical trials to have a higher frequency of gastrointestinal adverse reactions (such as abdominal pain and diarrhoea) than patients not receiving methadone. In a few cases, symptoms suggestive of opioid withdrawal when taking naloxegol 25 mg were observed in patients taking methadone for their pain condition. 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 naloxegol 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 naloxegol 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 12.5mg 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 naloxegol 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 rhinnorrhea, 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 Moventig and contact their physician.

Patients with CV conditions

Naloxegol 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. Moventig 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.

CYP3A4 inducers

Naloxegol is not recommended in patients who are taking strong CYP3A4 inducers (e.g. carbamazepine, rifampin, St. John's Wort) (see section 4.5).

For information regarding concomitant use with CYP3A4 inhibitors, see sections 4.2, 4.3 and 4.5.

Renal impairment

The starting dose for patients with moderate or severe renal insufficiency is 12.5 mg. If side effects impacting tolerability occur, naloxegol should be discontinued. The dose can be increased to 25 mg if 12.5 mg is well tolerated by the patient (see section 5.2).

Severe hepatic impairment

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

Cancer-related pain

There is limited clinical experience with the use of naloxegol in OIC patients with cancer-related pain. Therefore, caution should be used when prescribing naloxegol to such patients (see section 4.3).

Moventig contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per 12.5 mg / 25 mg tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction with CYP3A4 inhibitors and inducers

Interaction with strong CYP3A4 inhibitors

In an open-label, non-randomized, fixed-sequence, 3-period, 3-treatment, crossover study to evaluate the effect of multiple doses of ketoconazole on the single dose PK of naloxegol, 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 section 4.3). Grapefruit juice has been classified as a potent CYP3A4 inhibitor when consumed in large quantities. No data are available on the concomitant use of naloxegol with grapefruit juice. Concomitant consumption of grapefruit juice while taking naloxegol should generally be avoided and considered only in consultation with a healthcare provider (see section 4.3).

Interaction with moderate CYP3A4 inhibitors

In an open-label, nonrandomized, fixed-sequence, 3-period, 3-treatment, crossover study to evaluate the effect of multiple doses of diltiazem on the single dose PK of naloxegol, 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 section 4.2). The starting dose for patients

taking moderate CYP3A4 inhibitors is 12.5 mg once daily and the dose can be increased to 25 mg if 12.5 mg is well tolerated by the patient (see section 4.2).

No dosage adjustment is required for patients taking weak CYP3A4 inhibitors.

Interaction with strong CYP3A4 inducers
In an open-label, nonrandomized, fixed-sequence, 3-period, 3-treatment, single-dose, crossover study to evaluate the effect of multiple doses of rifampin on the single dose PK of naloxegol, co-administration of rifampin 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, Moventig is not recommended in patients who are taking strong CYP3A4 inducers (see section 4.4).

Interaction with P-gp inhibitors
A double-blind, randomized, 2-part, crossover, single centre study was conducted to evaluate the effect of quinidine on the pharmacokinetics of naloxegol and the effect of the co-administration of naloxegol and quinidine on morphine-induced miosis in healthy volunteers. 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 antagonize 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 Moventig 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 sections 4.2, 4.3 and 4.5).

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are limited data from the use of naloxegol in pregnant women.

Studies in animals have shown reproductive toxicity where systemic exposures were several times above the therapeutic exposure level (see section 5.3).

There is a theoretical potential for provoking opioid withdrawal in the foetus with use of an opioid receptor antagonist in the mother, who is being treated with a concurrent opioid. Naloxegol use is therefore not recommended during pregnancy.

Breast-feeding
It is unknown whether naloxegol is excreted in human milk. Available toxicological data in rats have shown naloxegol excreted in milk (see section 5.3).

At therapeutic doses, most opioids (e.g. morphine, meperidine, methadone) are excreted into breast milk in minimal amounts. 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 breast-feeding mothers is not recommended.

Fertility
The effect of naloxegol on fertility in humans has not been studied. Naloxegol was found to have no effect on fertility of male and female rats at oral doses up to 1,000 mg/kg per day (greater than 1,000 times the human therapeutic exposure (AUC) at the recommended human dose of 25 mg/day).

4.7 Effects on ability to drive and use machines

Moventig has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
In the pooled data from clinical trials the most commonly reported adverse reactions with naloxegol (≥ 5%) are: abdominal pain, diarrhoea, nausea, headache and flatulence. The majority of gastrointestinal adverse reactions were graded as mild to moderate, occurred early in treatment and resolved with continued treatment. They were often reported as having a component of cramping discomfort.

Tabulated list of adverse reactions
Adverse reactions are classified according to frequency and System Organ Class. Frequency categories are defined according to the following conventions: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data).

Table 1 Adverse reactions by System Organ Class (SOC) and frequency

System Organ Classification	Very Common	Common	Uncommon	Rare	Not known
Infections and Infestations		Nasopharyngitis			
Immune system disorders					Hypersensitivity
Nervous system disorders		Headache	Opioid withdrawal syndrome		
Gastrointestinal disorders	Abdominal pain[a], diarrhoea	Flatulence, nausea, vomiting			
Skin and subcutaneous tissue disorders		Hyperhidrosis			

Note: Selection of ADRs and their frequencies based on the 25 mg dose
[a] Reflects MedDRA Preferred Terms of: “abdominal pain”, “abdominal pain upper”, “abdominal pain lower” and “gastrointestinal pain”.

Description of selected adverse reactions
Opioid withdrawal syndrome
Naloxegol at therapeutic doses has minimal uptake across the blood brain barrier. In some patients, however, a constellation of symptoms has been reported, which resembles the syndrome of central opioid withdrawal. Most such reports were observed shortly after initial administration with the medicinal product and were mild or moderate in intensity.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Doses of naloxegol up to 1,000 mg were administered in healthy volunteers in clinical studies. 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 1,000 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 naloxegol 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 naloxegol, 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 naloxegol, symptomatic treatment as well as monitoring of vital functions should be performed.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for constipation, peripheral opioid receptor antagonists
ATC code: A06AH03

Mechanism of action and pharmacodynamic effects
Naloxegol is a PEGylated derivative of the mu-opioid receptor antagonist naloxone. PEGylation reduces naloxegol's passive permeability and also renders the compound a substrate for the P-glycoprotein transporter. 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.

In vitro studies demonstrate that naloxegol is a full neutral antagonist at the mu-opioid receptor. Naloxegol acts by binding to mu-opioid receptors in the GI tract targeting the underlying causes of OIC (i.e. reduced GI motility, hypertonicity and increased fluid absorption resulting from long-term opioid treatment).

Naloxegol functions as a peripherally-acting mu-opioid receptor antagonist in the gastrointestinal tract, thereby decreasing the constipating effects of opioids without impacting opioid-mediated analgesic effects on the central nervous system.

Clinical efficacy and safety
The efficacy and safety of naloxegol was established in two replicate double-blind, placebo-controlled studies in patients with OIC and non-cancer related pain (Kodiac 4 and Kodiac 5). 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. OIC was confirmed through a two week run in period and defined as < 3 spontaneous bowel movements (SBMs) per week on average with constipation symptoms associated with at least 25% of bowel movements. Patients were prohibited from using laxatives other than bisacodyl rescue laxative if they had not had a bowel movement for 72 hours. SBM was defined as a bowel movement without rescue laxative taken within the past 24 hours. Patients with mean Numeric Rating Scale (NRS) pain scores equal to or higher than 7 were not studied

due to the risk of confounding the efficacy result as a result of uncontrolled pain. Patients who had a QTcF >500 msec at screening, had a recent history of myocardial infarction within 6 months before randomization, had symptomatic congestive heart failure, or had any other overt CV disease were excluded from the clinical studies. In a thorough QT/QTc study, as defined by the ICH E14 Guideline, there were no clinically important changes in HR, RR, QT, PR or QRS intervals or T wave morphology observed. In addition, no safety and tolerability concerns were identified in this study up to the highest dose given (150 mg). According to the ICH E14 Guideline, this is considered a definitively negative thorough QT/QTc study. Patients with moderate or severe hepatic insufficiency (Child's-Pugh Class B or C) were excluded from the Phase III studies (Kodiac 4 and 5). Therefore, naloxegol has not been studied in OIC patients with moderate or severe hepatic impairment. Both studies were powered and stratified so that at least 50% of patients randomized to each treatment arm met baseline criteria to be categorized as a laxative inadequate responder (LIR).

Definition of laxative inadequate responder

To qualify as LIR, in the two weeks prior to first study visit patients had to have reported concurrent OIC symptoms of at least moderate severity while taking at least one laxative class for a minimum of four days during the pre study period.

Efficacy in the patient population targeted in this SmPC

Response over 12 weeks in the LIR group

Efficacy and durability of effect were measured in the primary end-point as response over the 12-week treatment period to naloxegol 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. The first of three multiplicity protected secondary endpoints was the 12-week responder rate in the LIR subgroup.

There was a statistically significant difference for the 25 mg dose versus placebo for the LIR subgroup responder rate in Kodiac 4 (p=0.002) and Kodiac 5 (p=0.014). Under multiplicity testing procedure, statistical significance for the 12.5 mg treatment group versus placebo in the LIR subgroup was observed in Kodiac 4 (p=0.028) but not in Kodiac 5 (p=0.074). In Kodiac 4, response rates in the placebo, 12.5 mg and 25 mg groups in the LIR subgroup were 28.8%, 42.6% and 48.7%, while in Kodiac 5, the corresponding response rates were 31.4, 42.4% and 46.8%. In the pooled data from Kodiac 4 and Kodiac 5, responder rates in the LIR subgroup were 30.1% for placebo, 42.5% for the 12.5 mg dose, and 47.7% for the 25 mg dose, with the relative risk (95% CI) for treatment effect versus placebo of 1.410(1.106, 1.797) and 1.584(1.253, 2.001) for the 12.5 mg and 25 mg groups, respectively.

Response over 12 weeks in patients with an inadequate response to at least two classes of laxative

Response to naloxegol over 12 weeks was tested in the sub-group of patients with inadequate response to at least two laxative classes, approximately 20% of the patients randomized. In a pooled analysis of Kodiac 4 and Kodiac 5 (90, 88 and 99 patients in the placebo, 12.5 mg and 25 mg groups respectively), higher response rates in this population was observed for the 25 mg dose group compared with placebo (p=0.040). The responder rates in this population were placebo 30.0%, 12.5 mg 44.3% and 25 mg 44.4%.

Time to first spontaneous bowel movement

The time to first SBM in the LIR subgroup after taking the first dose was shorter for the 25 mg dose as compared to placebo in Kodiac 4 (p<0.001) and Kodiac 5 (p=0.002). The 12.5 mg dose in the LIR subgroup also demonstrated shorter time to first post-dose SBM as compared to placebo in Kodiac 4 (p=0.002) and Kodiac 5 (p<0.001). In Kodiac 4, placebo, 12.5 mg and 25 mg dose had median time to first post dose SBM of 43.4, 20.6, and 5.4 hours, respectively. In Kodiac 5 the corresponding times to first post dose SBM were 38.2, 12.8, and 18.1 hours, respectively.

Mean number of days per week with at least one SBM

There was an increase in the mean number of days per week with at least one SBM in the LIR subgroup for the 25 mg dose in Kodiak 4 and Kodiac 5 (p<0.001 in both studies) and also for the 12.5 mg dose (p=0.006 in both studies).

OIC symptom improvement
The 25 mg dose in the LIR subgroup improved rectal straining (Kodiac 4 p=0.043, Kodiac 5 p<0.001). Stool consistency in the LIR subgroup as measured by the Bristol stool scale improved in Kodiac 5 versus placebo (p<0.001) but not in Kodiac 4 (p=0.156). The 25 mg dose in the LIR subgroup increased mean days per week compared with placebo with at least 1 complete spontaneous bowel movement (CSBM) in both studies (Kodiac 4 p=0.002, Kodiac 5 p<0.001).

Symptom responder end-point
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. In the LIR subgroup, the 25 mg dose increased the symptom responder rates in both studies as compared to placebo (Kodiac 4 p=0.001, Kodiac 5 p=0.005). The LIR subgroup symptom responder rates in Kodiac 4 for placebo, 12.5 mg and 25 mg arms were 24.6%, 36.5% and 45.3% and the symptom responder rates in Kodiac 5 were 25.6%, 33.6% and 42.7%.

Patient assessment of constipation symptoms (PAC-SYM) questionnaire
Naloxegol 25 mg dose in the LIR subgroup resulted in a greater improvement (change from baseline) of patient assessment of constipation symptoms (PAC-SYM) total scores compared with placebo in both studies at 12 weeks (Kodiac 4 p=0.023, Kodiac 5 p=0.002). The 12.5 mg dose in the LIR subgroup also resulted in greater improvement in total PAC SYM at week 12 compared with placebo in both studies (p= 0.020 and p=0.001 respectively). Naloxegol 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=0.004 and p<0.001, Kodiac 4 and 5, respectively) and for the stool domain scores in Kodiac 4 (p=0.031) and Kodiac 5 (p<0.001). There was no relevant impact on abdominal symptoms in either study (p=0.256 and p=0.916, Kodiac 4 and 5, respectively).

Potential for interference with opioid-mediated analgesia
There were no clinically relevant differences between naloxegol 12.5 mg, 25 mg, and placebo in average pain intensity, daily opioid dose or in opioid withdrawal scores over the 12-week study.

In the 12-week studies (Kodiac 4 and 5), the frequency of back pain AEs was 4.3% for naloxegol 25 mg versus 2.0% for placebo, and the frequency of extremity pain AEs was 2.2% for naloxegol 25 mg, versus 0.7% for placebo. In a long-term safety study (Kodiac 8), the frequency of AE reports of back pain was 8.9% for naloxegol 25 mg versus 8.8% for usual care. For extremity pain, the rate for naloxegol 25 mg was 3.5% versus 3.3% for usual care.

Safety and tolerability over an extended 12-week period
Kodiac 7 was a 12-week safety extension that allowed for patients from Kodiac 4 to continue the same blinded treatment from Kodiac 4 for an additional 12 weeks (placebo, naloxegol 12.5 mg or 25 mg daily). The primary objective was to compare safety and tolerability among the three treatment groups for an additional 12 weeks (beyond that observed in Kodiac 4) using descriptive statistics. In this study, naloxegol at doses of 12.5 mg and 25 mg was generally safe and well tolerated as compared with placebo in the treatment of OIC patients with non-cancer-related pain.

In all treatment groups, including placebo, improvements in PAC-SYM domains observed in Kodiac 4 were maintained for patients continuing in Kodiac 7.

Long-term safety and tolerability
Kodiac 8 was a Phase III, 52-week, multi-center, open-label, randomized, parallel group, safety and tolerability study of naloxegol versus usual care in the treatment of OIC in patients with non-cancer-related pain. The primary objective was to assess long-term safety and tolerability for naloxegol 25 mg and to compare with usual care treatment using descriptive statistics.

Eligible patients were randomized in a 2:1 ratio to receive either naloxegol 25 mg daily (qd) or usual care treatment for OIC for 52 weeks. Patients assigned to usual care followed a laxative treatment regimen for OIC determined by the investigator according to best clinical judgment, excluding peripheral mu-opioid receptor antagonists.

Of the 844 patients who were randomized, 61.1% completed the study (defined as completing the 2-week follow-up visit after the 52-week treatment period). Overall 393 and 317 patients had at least 6 and 12 months exposure to naloxegol 25 mg, respectively, in this study, which met the specified exposure requirements.

Long-term exposure to naloxegol 25 mg, up to 52 weeks, was generally safe and well tolerated in the treatment of OIC patients with non-cancer-related pain. During the 52-week treatment period there were no important unexpected differences in the safety and tolerability findings between the naloxegol 25 mg treatment group and the usual care treatment group.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies in opioid induced constipation with Moventig in children and adolescents aged 6 months to 18 years as per Paediatric Investigation Plan (PIP) decision (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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 an explanation as extensive biliary excretion was seen in the rat.

Food effects: A high-fat meal increased the extent and rate of naloxegol absorption. The C_{max} and area under the plasma concentration-time curve (AUC) were increased by approximately 30% and 45%, respectively.

Naloxegol as a crushed tablet mixed in water, given orally or administered through a nasogastric tube into the stomach, is bioequivalent to the whole tablet, with a median t_{max} of 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 NG tube, respectively.

Distribution
The mean apparent volume of distribution during the terminal phase (Vz/F) in healthy volunteers ranged from 968 to 2,140 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 effects 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%.

Biotransformation
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, oxidation and partial loss of the PEG chain. None of the metabolites were present in > 10% of the plasma concentrations of parent or total parent and metabolite related material.

Elimination
Following oral administration of radiolabelled 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.

Linearity/non-linearity
Across the range of doses evaluated peak plasma concentration and AUC increased in a dose-proportional, or approximately dose proportional, manner.

Special populations
Age and gender
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 elderly patients. Patients over 65 years of age have been represented in the phase III studies. Clinical studies of naloxegol did not include sufficient numbers of patients aged 75 years or over to determine whether they respond differently than younger patients, however, based on the mode of action of the active substance there are no theoretical reasons for any requirement for dose adjustments in this age group. For dose recommendations for patients with moderate or severe renal insufficiency, see section 4.2. There is no gender effect on the PK 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) and, therefore, no dose adjustment is necessary.

Body weight
Naloxegol exposure was found to increase with increased weight, however, the differences in exposure were not considered clinically relevant.

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 insufficiency is 12.5 mg. If side effects impacting tolerability occur, naloxegol should be discontinued. The dose can be increased to 25 mg if 12.5 mg is well tolerated by the patient (see section 4.2). Exposure of naloxegol in end-stage renal disease (ESRD) patients on haemodialysis was similar to healthy volunteers with normal renal function.

Hepatic impairment
Less than 20% decrease in AUC and 10% decrease 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 naloxegol was not evaluated. Use in patients with severe hepatic impairment is not recommended.

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

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and fertility.

Embryo-foetal development studies were conducted in rats and rabbits. A potentially treatment-related increased incidence of the skeletal variant bipartite vertebral centrum and a single foetus with anorchism was seen at the highest dose tested in the rat embryo-foetal development study. A possible treatment-related foetal skeletal malformation of fused arches was noted at highest dose tested in the rabbit embryo-foetal development study, in the absence of maternal toxicity. In a separate pre- and post-natal development study in rats, body weights were lower for male pups following maternal

administration at the high dose. All these effects were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Carcinogenicity studies of naloxegol were conducted in rats and mice. In male rats, a dose-related increase in Leydig cell adenomas and interstitial cell hyperplasia was observed at exposures considered sufficiently in excess of the maximum human exposure. The observed neoplastic changes are well known hormonal and centrally mediated effects in the rat which are not relevant for humans.

Studies in suckling rats have shown that naloxegol is excreted in the milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
mannitol (E421)
cellulose microcrystalline (E460)
croscarmellose sodium (E468)
magnesium stearate (E470b)
propyl gallate (E310)

Tablet coat
hypromellose (E464)
titanium dioxide (E171)
macrogol (E1521)
iron oxide red (E172)
iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Alu/alu blister.

12.5 mg film-coated tablets
Pack sizes of 30 and 90 film-coated tablets in non-perforated blisters.
Pack sizes of 30 x 1 and 90 x 1 film-coated tablets in perforated unit dose blisters.

25 mg film-coated tablets
Pack sizes of 10, 30 and 90 film-coated tablets in non-perforated blisters.
Pack sizes of 10 x 1, 30 x 1, 90 x 1 and 100 x 1 film-coated tablets in perforated unit dose blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Kyowa Kirin Holdings B.V.
Bloemlaan 2
2132NP Hoofddorp
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/962/001
EU/1/14/962/002
EU/1/14/962/003
EU/1/14/962/004
EU/1/14/962/005
EU/1/14/962/006
EU/1/14/962/007
EU/1/14/962/008
EU/1/14/962/009
EU/1/14/962/010
EU/1/14/962/011

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8 December 2014

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release
AstraZeneca AB
Gärtunavägen
SE-151 85 Södertälje
Sweden

AstraZeneca UK Limited
Silk Road Business Park
Macclesfield
SK10 2NA
United Kingdom

Piramal Healthcare UK Limited
Whalton Road
Morpeth
Northumberland, NE61 3YA
United Kingdom

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Moventig 12.5 mg film-coated tablets
Naloxegol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 12.5 mg naloxegol (as naloxegol oxalate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets
90 film-coated tablets
30 x 1 film-coated tablets
90 x 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Kyowa Kirin Holdings B.V.
Bloemlaan 2
2132NP Hoofddorp
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/962/001 30 film-coated tablets
EU/1/14/962/002 90 film-coated tablets
EU/1/14/962/008 30 x 1 film-coated tablets (unit dose)
EU/1/14/962/003 90 x 1 film-coated tablets (unit dose)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

moventig 12.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Moventig 25 mg film-coated tablets
naloxegol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 25 mg naloxegol (as naloxegol oxalate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

10 film-coated tablets
30 film-coated tablets
90 film-coated tablets
10 x 1 film-coated tablets
30 x 1 film-coated tablets
90 x 1 film-coated tablets
100 x 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Kyowa Kirin Holdings B.V.
Bloemlaan 2
2132NP Hoofddorp
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/962/004 10 film-coated tablets
EU/1/14/962/005 30 film-coated tablets
EU/1/14/962/006 90 film-coated tablets
EU/1/14/962/009 10 x 1 film coated tablets (unit dose)
EU/1/14/962/010 30 x 1 film-coated tablets (unit dose)
EU/1/14/962/007 90 x 1 film-coated tablets (unit dose)
EU/1/14/962/011 100 x 1 film-coated tablets (unit dose)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

moventig 25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

Blister perforated unit dose
Blister non-perforated

1. NAME OF THE MEDICINAL PRODUCT

Moventig 12.5 mg tablets
Naloxegol

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Kyowa Kirin

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

Blister perforated unit dose
Blister non-perforated

1. NAME OF THE MEDICINAL PRODUCT

Moventig 25 mg tablets
naloxegol

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Kyowa Kirin

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Moventig 12.5 mg film-coated tablets
Moventig 25 mg film-coated tablets

naloxegol

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Moventig is and what it is used for

Moventig contains the active substance naloxegol. It is a medicine used in adults to treat constipation specifically caused by pain medicines, called opioids, (e.g. morphine, oxycodone, fentanyl, tramadol, codeine) taken on a regular basis. It is used when laxatives 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 of the rectum, 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 a bowel movement, the feeling as if a stool is still in the rectum which needs to come out)

In patients taking opioids with constipation, who have tried at least one laxative and had incomplete relief of constipation, Moventig has been shown in clinical trials to increase the number of bowel movements and improve symptoms of constipation caused by opioids.

2. What you need to know before you take Moventig

Do not take Moventig:
- if you are allergic to naloxegol or similar medicines or any of the other ingredients of this medicine (listed in section 6).
- if your bowels are, or may be, blocked (obstructed) or you have been warned that your bowels are at risk of becoming blocked.

- if you have cancer in your gut or 'peritoneum' (the lining of your stomach area), advanced or recurrent ovarian cancer or if you are taking medicines used to treat cancer such as "VEGF inhibitors" (e.g. bevacizumab).
- if you are taking certain other medicines such as ketoconazole or itraconazole (to treat fungal infections), clarithromycin or telithromycin (antibiotics) or ritonavir, indinavir or saquinavir (to treat HIV).

Do not use Moventig if any of the above applies to you. If you are not sure, talk to your doctor, pharmacist or nurse before taking Moventig.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Moventig:
- if you have stomach ulcers, Crohn's Disease (an illness where your gut is inflamed), diverticulitis (another illness where your gut is inflamed), cancer in your gut or 'peritoneum' (the lining of your stomach area), or any conditon that might damage the wall of your bowel
- if you currently have unusually severe, persistent or worsening stomach pain
- if the natural protective barrier between the blood vessels in the head and in the brain is damaged, for example if you have cancer in the brain or the central nervous system, or if you have a disease of the central nervous system like multiple sclerosis or Alzheimer's disease – contact your doctor immediately if you experience lack of pain relief from your opioid medicine or symptoms of opioid withdrawal syndrome (see section 4).
- if you are taking methadone (see section below "Other medicines and Moventig")
- if you have had a heart attack within the last 6 months, have heart failure with daily shortness of breath or other severe problems with your heart which cause daily symptoms
- if you have kidney problems – your doctor may tell you to take a different dose (see section below "How to take Moventig")
- if you have severe liver illness
- if you have cancer-related pain

If any of the above apply to you, or you are not sure, talk to your doctor, pharmacist or nurse before taking Moventig.

Talk to your doctor, pharmacist or nurse whilst taking Moventig:
- if you develop severe, persistent or worsening stomach pain. This could be a symptom of damage to the wall of the gut. Tell your doctor immediately, you may need a lower dose or to stop taking Moventig.
- if your opioid medicine is to be stopped for more than 24 hours
- if you experience symptoms of opioid withdrawal syndrome (see section below "Possible side effects"). Tell your doctor, you may need to stop taking Moventig.

Children and adolescents
Moventig is not recommended for use in children and adolescents below 18 years of age because it has not been studied in these age-groups.

Other medicines and Moventig
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Tell your doctor what opioid pain medicines you are taking and the dose of them.

Do not take Moventig if you are taking any of the following medicines (see section "Do not take Moventig"):
- ketoconazole or itraconazole - to treat fungal infections
- clarithromycin or telithromycin - antibiotics
- ritonavir, indinavir or saquinavir – to treat HIV

Do not take Moventig if any of the above apply to you.

Tell your doctor, pharmacist or nurse if you are taking any of the following medicines:
- other medicines for constipation (any laxatives)
- methadone
- diltiazem or verapamil (for high blood pressure or angina). You may need to take a lower dose of Moventig
- rifampin (an antibiotic), carbmazepine (for epilepsy) or the herbal medicine St. John's wort (for depression). You may need to stop taking Moventig.

If any of the above apply to you, or you are not sure, talk to your doctor, pharmacist or nurse before taking Moventig.

Moventig with drink
You should not drink large amounts of grapefruit juice whilst taking Moventig. This is because large amounts can affect how much of the naloxegol medicine gets into the body.

Pregnancy and breast-feeding
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor, pharmacist or nurse for advice before taking this medicine. The use of Moventig during pregnancy is not recommended.

Do not use Moventig during breast-feeding.

Driving and using machines
Moventig is not expected to affect you being able to drive a car or use any tools or machines.

Moventig contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per 12.5 mg / 25 mg tablet, that is to say essentially 'sodium-free'.

3. How to take Moventig

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is 1 tablet of 25 mg each day.

Take Moventig in the morning, to avoid bowel movements in the middle of the night. Moventig should be taken on an empty stomach at least 30 minutes before the first meal of the day or 2 hours after the first meal.

When treatment with Moventig is started, all currently used laxatives should be stopped, until instructed by your doctor to restart.

Your doctor may tell you to take a lower dose of 12.5 mg
- if you have kidney problems
- if you take diltiazem or verapamil (for high blood pressure or angina)

Your doctor may tell you to increase the dose to 25 mg depending on how you respond to the medicine.

If you have trouble swallowing the tablet
If you have trouble swallowing the tablet you can crush it and mix with water as follows:
- Crush the tablet to a powder
- Pour the powder into half a glass of water (120 ml)

- Stir and drink immediately
- To make sure there is no medicine left, rinse the empty glass with another half a glass of water (120 ml), and drink it

If you take more Moventig than you should
If you take more Moventig than you should, talk to a doctor or go to hospital.

If you forget to take Moventig
- If you miss a dose of Moventig, take it as soon as you remember. However, if it is less than 12 hours until your next dose, skip the missed dose.
- Do not take a double dose to make up for a missed dose.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side effects may happen with this medicine:

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

Common (may affect up to 1 in 10 people):
- passing wind
- nausea (feeling sick to the stomach)
- vomiting
- nasopharyngitis (runny or stuffy nose)
- headache
- excessive sweating

Uncommon (may affect up to 1 in 100 people):
- opioid withdrawal symptoms (if you have a combination of three or more of these symptoms: feeling depressed, nausea, vomiting, diarrhoea, excess sweating, muscle aches, increased tearing, insomnia, yawning, fever) which would usually occur within the first few days after starting naloxegol.

Not known (frequency cannot be estimated from the available data):
- allergic reaction

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Moventig

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after “EXP”. The expiry date refers to the last day of that month.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Moventig contains

- The active substance is naloxegol.
  - Each Moventig 12.5 mg film-coated tablet (tablet) contains 12.5 mg naloxegol as naloxegol oxalate.
  - Each Moventig 25 mg film-coated tablet (tablet) contains 25 mg naloxegol as naloxegol oxalate.
- The other ingredients are:
  - tablet core: mannitol (E421), cellulose microcrystalline (E460), croscarmellose sodium (E468), magnesium stearate (E470b), propyl gallate (E310)
  - film-coating: hypromellose (E464), titanium dioxide (E171), macrogol (E1521), iron oxide red (E172) and iron oxide black (E172).

What Moventig looks like and contents of the pack

Moventig 12.5 mg: a mauve coloured, oval, dimensions 10.5 x 5.5 mm film-coated tablet, marked “nGL” on one side and “12.5” on the other side.

Moventig 25 mg: a mauve coloured, oval, dimensions 13 x 7 mm, film-coated tablet, marked “nGL” on one side and “25” on the other side.

Moventig 12.5 mg tablets are available in aluminium blisters in pack sizes of 30 or 90 film-coated tablets in non-perforated blisters and 30x 1 or 90x1 film-coated tablets in perforated unit dose blisters.

Moventig 25 mg tablets are available in aluminium blisters in pack sizes of 10, 30 or 90 film--coated tablets in non-perforated blisters and 10x1, 30x1, 90x1 or 100x1 film-coated tablets in perforated unit dose blisters.

Not all pack sizes may be marketed in your country.

Marketing Authorisation Holder

Kyowa Kirin Holdings B.V.
Bloemlaan 2
2132NP Hoofddorp
The Netherlands

Manufacturer

AstraZeneca AB
Gärtunavägen
SE-151 85 Södertälje
Sweden

AstraZeneca UK Limited
Silk Road Business Park
Macclesfield
SK10 2NA
United Kingdom

Piramal Healthcare UK Limited
Whalton Road

Morpeth
Northumberland, NE61 3YA
United Kingdom

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Kyowa Kirin Ltd
Verenigd Koninkrijk/Royaume-Uni/Vereinigtes Königreich
Tel/Tél: + 44 (0)1896 664000

Lietuva
Kyowa Kirin Ltd
Didžioji Britanija *(Jungtinė Karalystė)*
Tel: + 44 (0)1896 664000

България
Kyowa Kirin Ltd
Великобритания (Обединеното кралство)
Тел.: + 44 (0)1896 664000

Luxembourg/Luxemburg
Kyowa Kirin Ltd
Royaume-Uni/Vereinigtes Königreich
Tel/Tél: + 44 (0)1896 664000

Česká republika
Novatin s.r.o.
Tel: + 420257 217 762

Magyarország
Kyowa Kirin Ltd
Egyesült Királyság *(Nagy-Britannia)*
Tel: + 44 (0)1896 664000

Danmark
Kyowa Kirin filial af Kyowa Kirin AB
Sverige
Tlf: +46 8 50 90 74 10

Malta
Novatin Ltd.
Tel: +356 21375788

Deutschland
Kyowa Kirin GmbH
Tel: +49 (0) 211/416 119-0

Nederland
Kyowa Kirin Pharma BV
Tel: +31 (0)900 1231236

Eesti
Kyowa Kirin Ltd
Ühendkuningriik
Tel: + 44 (0)1896 664000

Norge
Kyowa Kirin filial av Kyowa Kirin AB
Sverige
Tlf: +46 8 50 90 74 10

Ελλάδα
ΑΝΑΒΙΩΣΙΣ ΙΚΕ
Τηλ: +30 2102711020

Österreich
Kyowa Kirin GmbH
Deutschland
Tel: +49 (0) 211/416 119-0

España
Kyowa Kirin Farmacéutica S.L.U
Tel: +34 91 534 37 10

Polska
Kyowa Kirin Ltd
Wielka Brytania
Tel: + 44 (0)1896 664000

France
Kyowa Kirin Pharma SAS
Tél : +33 (0)1 55 39 14 30

Portugal
Kyowa Kirin Farmacêutica, Unip. Lda.
Tel: +351 218 700 002

Hrvatska
Novatin d.o.o.

România
Kyowa Kirin Ltd

Tel: + 385 1 2347 074

Ireland
Kyowa Kirin Ltd
United Kingdom
Tel: + 44 (0)1896 664000

Ísland
Kyowa Kirin Ltd
c/o Icepharma hf
Sími: +354 5408000

Italia
Kyowa Kirin S.r.l
Tel: +39 02 92169424

Κύπρος
CENTROM PHARMA LIMITED
Τηλ: + 357 22 283565

Latvija
Kyowa Kirin Ltd
Lielbritānija
Tel: + 44 (0)1896 664000

Marea Britanie
Tel: + 44 (0)1896 664000

Slovenija
Novatin s.r.o.
Češka
Tel: + 420257 217 762

Slovenská republika
Novatin s.r.o.
Česká republika
Tel: + 420257 217 762

Suomi/Finland
Kyowa Kirin Ab filial i Finland
Puh/Tel: +358 10 23 55 560

Sverige
Kyowa Kirin AB
Tel: +46 8 50 90 74 10

United Kingdom
Kyowa Kirin Ltd
Tel: + 44 (0)1896 664000

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.