EU Risk Management Plan

for

Moventig (naloxegol)

RMP version to be assessed as part of this application:	Version 8.2
Data lock point for this RMP	15 September 2021
Date of final sign off	13 November 2023
Rationale for submitting an updated RMP	The RMP update is required as part of the Type-II variation Amendment of SmPC (Summary of Product Characteristics) following the class recommendations of other Peripherally-Acting Mu-Opioid Receptor Antagonists (PAMORA) medicinal products and new data available from recently completed 3 Real World Evidence (RWE) studies in patients treated with Naloxegol for Opioid Induced Constipation (OIC) with underlying cancer-related pain.

Summary of significant changes in this RMP:

- Update to clinical trial exposure
- Update to post-marketing exposure
- Update to the characterization of identified and potential risks
- Removal of Safety in Patients with Cancer Pain as Missing information based on the new data available from recently completed 3 Real World Evidence (RWE) studies in patients treated with Naloxegol for OIC with underlying cancer-related pain.

Other RMP versions under evaluation	Not applicable
Details of the currently approved RMP	Version 7.2
QPPV name	Beatriz Mengotti Fernandez de los Rios

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's EU QPPV. The electronic signature is available on file.

Table of Contents

List of Tables

List of Abbreviations

Abbreviation/Special term	Definition/Explanation
ADR	Adverse drug reaction
AE	Adverse event
AUC	Area under the curve
BBB	Blood brain barrier
BMI	Body Mass Index
CDS	Core Data Sheet
CI	Confidence Interval
C_{max}	Maximum concentration
CNS	Central Nervous System
CRC	Concurrent Reference Cohort
CV	Cardiovascular
CV-EAC	Cardiovascular-Event Adjudication Committee
CYP3A4	Cytochrome P450 3A4
DSUR	Development Safety Update report
DUS	Drug Utilisation Study
EEA	European Economic Area
EU RMP	European Union Risk Management Plan
GI	Gastrointestinal
hERG	Human either-a-go-go-related gene
MACE	Major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
MRHD	Maximum Recommended Human Dose
NIC	Naloxegol Inception Cohort

Abbreviation/Special term	Definition/Explanation
NOAEL	No-Observed-Adverse-Effect-Level
NSAIDs	Non-steroidal anti-inflammatory drugs
OIC	Opioid Induced Constipation
PAMORA	Peripherally-Acting Mu-Opioid Receptor Antagonists
PASS	Post-Authorisation Safety Study
PBRER	Periodic Benefit Risk Evaluation Report
P-gp	P glycoprotein
PIL	Patient information leaflet
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic
PL	Product label
PSUR	Periodic Safety Update Report
PT	MedDRA Preferred Term
RMM	Risk minimisation measures
RMP	Risk Management Plan
RR	Relative risk
SAE	Serious adverse event
SmPC	Summary of Product Characteristics (EU)
UC	Usual-care
UK	United Kingdom
US	United States

1. PART I: PRODUCT OVERVIEW

Table 1: Product Overview

Active substance(s) (INN or common name)	Naloxegol
Pharmacotherapeutic group(s) (ATC Code)	A06AH03
Marketing Authorisation Holder	Kyowa Kirin Holdings B.V.
Medicinal products to which this RMP refers	Moventig 12.5 mg film-coated tablets Moventig 25 mg film-coated tablets
Invented name in the European Economic Area (EEA)	MOVENTIG™
Brief description of the product	**Chemical class**: Peripherally acting mu-opioid receptor antagonist (PAMORA). Naloxegol is a PEGylated derivative of the mu-opioid receptor antagonist naloxone
	Summary of mode of action: PEGylation reduces naloxegol's passive permeability and also renders the compound a substrate for the P glycoprotein (P-gp) transporter. Due to poorer permeability and increased efflux of naloxegol across the blood-brain barrier (BBB), related to P-gp substrate properties, the central nervous system (CNS) penetration of naloxegol is minimal.
Indication(s)	Current: Naloxegol is indicated for the treatment of Opioid-Induced Constipation (OIC) in adult patients who have had an inadequate response to laxative(s)
Dosage	Current: 25 mg once daily oral route.
Pharmaceutical form(s) and strengths	• 12.5 mg film-coated tablet – oval, 10.5 x 5.5 mm, colour mauve. • 25 mg film-coated tablet – oval, 13 x 7 mm, colour mauve. Tablets are engraved with "nGL" on one side and the tablet strength on the other.
Is/will the product be subject to additional monitoring in the EU?	Yes

2. PART II: SAFETY SPECIFICATION

2.1 PART II: Module SI – Epidemiology of the indication and target population

2.1.1 Opioid-induced constipation (OIC)

2.1.1.1 Incidence

Currently, there is limited observational data estimating the incidence of OIC. The observational study data that are available were derived from three studies conducted within a United Kingdom (UK) or United States (US) electronic healthcare database. Results reported from electronic healthcare database study are of limited value with respects to estimating incidence of OIC. Specifically, diagnosis codes specific to OIC are either non-existent or rarely used given the underlying purpose of the database (e.g., billing reimbursement in the United States).

Consistent estimates of OIC incidence were not observed in externally reported clinical trials. Incidence estimates across trials ranged from 0.7% to 51.7% and differed as much as 4% to 26% within a trial. (See Wirz et al 2008, Wallace et al 2009, Flogegard and Ljungman 2003, Ruoff et al 2003, Caldwell et al 2002, Payne et al 2001, Goldblum 2000, Hale et al 2009, Hartrick et al 2009, Karlsson and Berggren 2009, Perrot et al 2006, Gilron et al 2005, Likar et al 2006). The recently published European expert consensus statement which focused on the pathophysiology and management of opioid-induced constipation reported that OIC occurs in 51-87% of patients receiving opioids for cancer and between 41-57% patients receiving opioids for chronic non-cancer pain (Farmer et al, 2018).

2.1.1.2 Prevalence

Identifying a consistent estimate is more challenging given methodological differences across population-based studies. Definition of constipation, data source and type of opioid are just a few of the differences that may impact the estimates. Population heterogeneity is another factor that may impact the prevalence estimates of OIC. For example, cancer patients tend to suffer from constipation, regardless of pain management due to metabolic changes, dehydration and/or decreased mobility (Pappagallo 2001). The inconsistency between estimates are highlighted in a review where the authors evaluated 16 studies, clinical trials and observational, to report a range of OIC prevalence between 15-95% within the given study population (Boswell et al 2010). Given these challenges, estimates for prevalence of OIC should be qualified according to the population of interest. US-based observational studies estimate the prevalence of OIC in non-cancer pain patients to range between 17-57% (Brown et al 2006, Mahowald et al 2005, Cook et al 2008). An elevated prevalence of OIC (60-95%) as well as regional inconsistency was observed for cancer pain, as reported by European- and US-based observational

studies (Boswell et al 2010, Droney et al 2008, Lundorff et al 2008, Braiteh et al 2007, Sykes 1998, Meuser et al 2001). Cancer populations are more likely to be exposed to morphine than other opioids (Pergolizzi et al 2008, Salvato et al 2003), which may partially contribute to the higher constipation rates observed in these studies. Within the ranges reported by underlying disease, prevalence may differ by type of opioid and frequency of opioid use. This additional level of heterogeneity was demonstrated in a population-based survey conducted among 2055 adults taking chronic opioids for pain management of non-cancerous conditions where a prevalence of 67% was reported in patients utilizing morphine and 17% to 34% for patients treated with other opioids (oxycodone, codeine, hydrocodone, propoxyphene, tramadol) (Cook et al 2008). Finally, heterogeneity in prevalence estimates can be observed within opioid use patterns where a prevalence study conducted among patients with chronic non-cancer pain reported constipation related to chronic daily opioid use in 39% of patients versus 27% among patients on intermittent opioid use (p=0.05) (Brown et al 2006).

2.1.1.3 Demographics of the population in the authorised indication and risk factors for the disease

Two US administrative claims-based observational studies of patients utilizing opioids chronically for non-cancer pain provide some insight into the demographic profile from which OIC patients originate. One study described patients in a privately and publicly insured population where both populations were mostly female (private=59%, public=72%) with an average of 50 and 53 years, respectively (Braden et al 2008). Similar demographic characteristics (63% female, average age of 57 years) were reported among privately insured patients dispensed opioids for ≥180 days per year (Cicero et al 2009). Survey based studies in the US provided additional demographic detail of chronic opioid users. The majority of patients using opioids “at least several times a week for a month or more” are female (60.9%), white (87.8%), aged 30-45 years (37.1%), married (66.9%), and have received a maximum of a high school diploma (67.3%) (Hudson et al 2008). Separate AstraZeneca-initiated UK and German electronic healthcare database studies among adult patients (≥18 years of age) utilizing chronic opioids (≥183 days of continuous use) reported the study populations to be mostly female (>67%) with a median age of 66 and 76, respectively (internal data).

Given the condition, OIC, is a side-effect of opioid exposure, risk factors in this case must be a component of the opioid exposure. Specifically, type of opioid, dosing frequency, and route of administration are risk factors for opioid-induced constipation. A population-based survey conducted among 2,055 adults taking chronic opioids for pain management of non-cancerous conditions reported a prevalence of 67% in patients utilizing morphine and 17% to 34% for patients

treated with other opioids (oxycodone, codeine, hydrocodone, propoxyphene, tramadol). In addition, a prevalence study conducted among patients with chronic non-cancer pain reported constipation related to chronic daily opioid use in 39% of patients versus 27% among patients on intermittent opioid use (p=0.05) (Brown et al 2006). Oral administration may be associated with a higher risk of developing OIC. Oral administration appears to cause more constipation than intravenous, intramuscular, epidural, subcutaneous or transdermal administration, which are broadly equivalent (Hanks et al 2001). Several studies have shown that the risk of OIC was higher with oral morphine compared with transdermal fentanyl (p<0.001). (See Allan et al 2001, Ahmedzai and Brooks 1997, Hanks et al 2001, Staats et al 2004, Tassinari et al 2008, Donner et al 1996.)

2.1.1.4 The main existing treatment options

The recently published "Pathophysiology and management of opioid-induced constipation: European expert consensus statement", is the first evidence-based guideline for managing OIC. The guidelines recommend that a step-wise approach is used in the management of OIC. When a patient reports constipation, the first step would be to address lifestyle aspects, in order to assess if there are alternative reasons for the constipation such as psychological aspects, inactivity, concomitant medications or metabolic abnormalities. Standard laxatives such as osmotic agents and stimulants are good first-line choices in the next step of the management of OIC. If laxatives are ineffective and the constipation is clearly related to commencing, escalating or a switch in opioids, then an opioid-receptor antagonist would be the next step as these are known to alleviate the adverse effects of opioids. Several opioid antagonists with local action within the gut or peripherally-acting mu-opioid receptor antagonists (PAMORAs), such as naloxegol, have become available, and these have been shown to be safe and effective in treating OIC.

Another generally accepted approach to management of constipation is as follows (World Gastroenterology Organisation 2010, Leppert 2010, Thomas and Cooney 2008): 1) Non-pharmacologic treatment strategies include increasing fluid intake, dietary fibre, or exercise; 2) Pharmacologic treatment strategies that do not involve altering the current opioid regimen for pain management which include the use of over-the-counter laxatives (stool softeners, stimulant laxatives, osmotic laxatives or bulk-forming laxatives); 3) Prescription treatments, such as opioid-receptor antagonists which target the underlying cause of opioid-induced constipation, lubiprostone which activates chloride channels to promote fluid secretion into the intestinal lumen, or plecanatide, a guanylate cyclase-C agonist can be used in the event the 'desired result' is not achieved with other therapeutic options. If oral laxatives are found to be ineffective, rectal measures may be introduced. In

emergency situations, medical procedures such as bowel disimpaction in a hospital setting can be utilized to resolve constipation.

Given that traditional laxatives do not target μ-opioid receptors, evidence from observational studies suggests that traditional laxatives are insufficient to prevent or alleviate the symptoms of OIC for many patients (Brock et al 2012). The PROBE 1 survey of patients taking oral opioids and laxatives in the US and EU (n=322) reported that, despite these patients taking laxatives, the majority (81%) of patients were still experiencing constipation, 45% reported <3 bowel movements per week, and 58% reported straining (Bell et al 2009). A separate US-based survey of opioid treated patients reported laxative therapy to be sub-optimal with 46% of patients not achieving the desired treatment outcome >50% of the time (Pappagallo 2001).

2.1.1.5 Natural history of the indicated condition in the untreated population, including mortality and morbidity

In some patients, OIC may become so severe and distressful that patient may taper or even discontinue opioid use in an attempt to relieve their discomfort, as they prefer tolerating their pain rather than suffering from continued bowel dysfunction (Panchal et al 2007, Mueller-Lissner 2010, Hjalte et al 2010). OIC is one of the most common reasons why patients stop opioid treatment regimens (Bell et al 2009). However, this compromises effective analgesia, leading to a return of the pain being treated (Bell et al 2009, Dhingra et al 2013, Panchal et al 2007). It has also been suggested that some patients receiving long-term opioid treatment for any type of pain would rather endure their pain rather than the constipation opioids may cause (Panchal et al 2007).

The PROBE 1 survey of patients taking oral opioids and laxatives in the US and EU (n=322) reported that one-third of patients missed, decreased, or stopped using opioids specifically in order to ease defecation and pass a bowel movement (Bell et al 2009). In addition, 92% of patients subsequently reported that they experienced increased pain after doing so (Bell et al 2009). A small qualitative US self-reported survey of advanced cancer patients with OIC (n=12) indicated decreasing or stopping the use of opioid medications to relieve OIC is common, indicating that OIC may be a prominent barrier to effective pain management (Dhingra et al 2013).

To our knowledge, there is no published epidemiologic literature that describes mortality rate within OIC patients or directly explores the relationship between OIC and mortality. Looking beyond OIC, two observational studies using US administrative claims databases evaluated risk of safety events among elderly patients treated with opioid therapy (Solomon et al 2010b, Solomon et al 2010a). One of the studies reported incidence rates for all-cause mortality, death related to an adverse event, and out-of-hospital-cardiac death equal to 75, 12, and 17 per

1000-person years, respectively (Solomon et al 2010b). When compared to non-selective non-steroidal anti-inflammatory drugs (NSAIDs) using a propensity score matched analysis for baseline characteristics, the same study reported that opioid therapy is associated with an increased risk of all-cause mortality (Hazard Ratio=1.87, 95% confidence interval [CI]: 1.39-2.53) and out-of-hospital death (Hazard Ratio 1.96, 95% CI: 1.05-3.67) (Solomon et al 2010b). The second study indicated that the type of opioid impacts mortality, with risk increased in oxycodone users RR 2.43; 95%CI 1.47-4.00) and codeine relative risk (RR) 2.05 (95% CI: 1.22-3.45) versus hydrocodone (Solomon et al 2010a).

2.1.1.6 Important co-morbidities

To our knowledge, there is no published literature of observational studies describing co-morbidities of patients with OIC; however, published literature (Hudson et al 2008, Cicero et al 2009, Carman et al 2011) describing epidemiological studies and surveys of chronic opioid users and patients newly initiating chronic opioid therapy, as well as an observational study assessing the burden of OIC, reported the following baseline/concurrent conditions:

- **Pain**, including arthritis or rheumatism, chronic back problems, migraine/chronic headaches, dorsalgia, pain syndrome, and neuralgia.
- **Cardiovascular conditions**, including hypertension, ischaemic heart disease, angina, and heart failure.
- **Endocrine/Metabolic conditions**, including type 2 diabetes mellitus, hyperthyroidism, and hyperlipidaemia/ hypercholesterolemia.
- **Gastrointestinal conditions**, including stomach ulcer/enteritis, urination/bladder problems, urinary tract infection, and gastro-oesophageal reflux disease.
- **Respiratory conditions**, including asthma, chronic obstructive pulmonary disease, dyspnoea, and acute respiratory infection.
- **Psychiatric conditions**, including major depressive disorder, anxiety, and substance abuse.

2.2 PART II: Module SII – Non-clinical part of the safety specification

2.2.1 Toxicity

Key issues identified from acute or repeat-dose toxicity studies

The liver was identified as a target organ of toxicity in chronic studies (weight increase and hypertrophy in rodents, weight increase in dogs). The liver findings were slight, reversible, non-adverse in nature and occurred at significant margins to clinically relevant exposures indicating little relevance to man. There has been no liver signal observed in clinical trials.

Reproductive and developmental toxicity

Naloxegol did not impair fertility in rats. Any potentially naloxegol-mediated effects in the reproductive/development studies were seen at significant maternal exposure margins of at least 79x to the maximum recommended human dose (MRHD). The relevance of the observed developmental effects observed in rats and rabbits to human safety is considered negligible since they occurred at maternal exposures that are not clinically relevant.

Genotoxicity

Naloxegol oxalate did not show any mutagenic activity in a bacterial mutation (Ames) test. Naloxegol (free base) 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 supports the conclusion that naloxegol is not genotoxic

Carcinogenicity

Neoplastic changes were observed in rats and are well known hormonal and centrally- mediated effects that are known not to translate to man. Naloxegol does not have any carcinogenic potential relevant for humans.

2.2.2 Safety pharmacology

Cardiovascular system including potential effect on the QT interval

Cardiovascular effects were noted in the dog telemetry study and were limited to moderate decreases in arterial blood pressure, left ventricular systolic pressure and indices of cardiac contractility. The no-observed-adverse-effect-level (NOAEL) for these effects was at an exposure (maximum concentration [Cmax]) comparable to

human exposure at the MRHD. However, cardiovascular effects were not seen in the isolated dog myocyte or rat isolated heart and naloxegol was only a weak inhibitor of the human ether-a-go-go-related gene (hERG) ion channel (IC50>300μM) and was inactive at a further 7 cardiac ion channels.

The telemetry findings in the dog study are unlikely to be of clinical relevance. There has been no clear or consistent cardiovascular-type safety signal observed in clinical trials.

Gastrointestinal system

Naloxegol decreased gastric emptying and intestinal transport. The NOAEL was 15 times and 112 times the human exposure (Cmax) at MRHD for gastric emptying and intestinal transport, respectively. Gastrointestinal effects occurred at significant margins to clinically relevant exposures indicating little relevance to man.

Nervous system

Naloxegol did not show any central nervous system (CNS) effects, including any potential abuse or drug dependence liability. At clinically relevant doses, naloxegol administration is not expected to cause any CNS effects and has no abuse potential or drug dependence liability.

Renal system

Mild to moderate effects on renal function were noted. The NOAEL was 347 times the human exposure (Cmax). Renal effects occurred at significant margins to clinically relevant exposures indicating little relevance to man.

2.3 PART II: Module SIII: Clinical trial exposure

2.3.1 Summary of clinical trial exposure

Overall cumulative subject exposure are provided in Table 2, based on actual exposure data from completed interventional clinical trials and 1 ongoing phase I interventional study paediatric study, which currently has 46 patients treated (33 female patients and 13male patients as of 15-Sep-2021, D3820C00016). The completed studies are Phase IIb Study 07-IN-NX003 and Phase III Studies D3820C00004, D3820C00005, D3820C00006, D3820C00007, D3820C00008.

Additionally, study D3820C00006 (n=13), on OIC patients with cancer pain, ended enrolment early due to slow recruitment. The decrease in the number of patients exposed for ≥50 weeks to ≥52 weeks is mainly due to the treatment completion visit schedule and not due to discontinuations in Study D3820C00008.

Additionally, study D3820R00009, on OIC patients with cancer pain, was discontinued due to low patient accrual, time required to reach target patient numbers, inability to obtain all required data from data sources, limited options for additional data sources (other sources alongside the THIN, PHARMO and GePaRD databases were also assessed for feasibility), and inability to adapt or reduce target patient numbers (considered as not scientifically feasible or statistically valid).

Cumulative summary tabulations of exposure by age/gender and by racial group are presented in

Table **3** and Table 4 respectively. Exposure by dose is presented in Table 5. All numbers provided in the below tables are derived from completed studies (Phase IIb Study 07-IN-NX003 and Phase III Studies D3820C00004, D3820C00005, D3820C00006, D3820C00007, D3820C00008) and 1 ongoing study D3820C00016.

Table 2: Cumulative Duration of Exposure to Naloxegol

Duration of exposure	**Subjects n (%)**
< 4 Weeks	155 (8.8)
≥4 Weeks	171 (9.7)
≥12 Weeks	1,044 (59.2)
≥ 24 Weeks	65 (3.7)
≥50 Weeks	245 (13.9)
≥ 52 Weeks	85 (4.8)
Total	**1,765**

Table 3:Cumlative Exposure to Naloxegol by Age group and Gender

	Number of subjects		
Age range (years)	**Male**	**Female**	**Total**
≤18	12	33	45
>18 to ≤40	33	65	98
41 to 50	72	153	225
51 to 60	121	218	339
≥61	70	101	171
Missing[a]	341	546	891
Total	**649**	**1,116**	**1,765**

a- Age group by gender patient exposure data was not available for studies D3820C00004 and D3820C00005, hence only gender exposure data has been provided.

Table 4:Cumulative Exposure to Naloxegol from Ongoing and Completed Clinical Trials by Racial Group

Racial group	Number of subjects
American Indian or Alaska Native	7
Asian	11
Black or African American	318
Native Hawaiian or other Pacific Highlander	1
Not Allowed to Ask per Local Regulation	1
Other	14
White	1,408
Missing[a]	5
Total	**1,765**

a-The subjects with missing race category are from ongoing study D3820C00016.

Table 5: Cumulative Exposure to Naloxegol by Dose

Dose of Exposure	Patients n (%[a])
Naloxegol 5 mg	32 (1.8)
Naloxegol 12.5 mg	566 (32.1)
Naloxegol 25 mg	1,131 (64.1)
Naloxegol 50 mg	36 (2.0)
Total	**1,765**

[a] Percentages are based on the total number of unique patients (n=1765). Patients (n=16) who received naloxegol 12.5 mg in the 12-week studies (D3820C00004, D3820C00005) and naloxegol 25 mg in the 52-week study (D3820C00008) are counted under both doses.

2.4 PART II: Module SIV – Populations not studied in clinical trials

2.4.1 Exclusion Criteria in pivotal clinical studies within the development programme

Important exclusion criteria in the pivotal clinical studies are described in Table 6 below.

Table 6: Exclusion criteria in pivotal clinical studies

Criteria	Reason for exclusion	Is it considered to be included as missing information?
Conditions that increase the risk of gastrointestinal (GI) perforation	Patients were excluded from the clinical trials because they were at increased risk for GI perforation, a fatal adverse reaction observed with a structurally similar drug, methylnaltrexone. GI perforation can also rarely be caused by prolonged constipation resulting from chronic opiate therapy.	No. Rationale: Naloxegol is contraindicated in patients with known or suspected GI obstruction or in patients at increased risk of recurrent obstruction, due to the potential for GI perforation. Therefore, use in this population of patients is not relevant for inclusion as missing information.
Patients receiving opioid treatmentfor cancer pain	Patients with cancer pain may be receiving treatment for the cancer and not taking a stable regimen of opioids. Therefore, these patients were excluded to avoid factors that might confound a complete understanding of the safety and efficacy of naloxegol	No. Rationale: Data from over 500 patients treated in a real world setting (KYONAL,NACASY, MovE) • Cobo Dols 2021 One-year efficacy and safety of naloxegol on symptoms and quality of life related to opioid-induced constipation in patients with cancer: KYONAL study. • Davies 2022. A prospective, real-world, multinationals

Criteria	Reason for exclusion	Is it considered to be included as missing information?
		Study of naloxegol for patients with cancer pain diagnosed with opioid-induced constipation: NACASY Study. • Lemaire 2021. Effectiveness of naloxegol in patients with cancer pain suffering from opioid-induced constipation: MovE Study. • Ostan 2021. Can naloxegol therapy improve quality of life in patients with advanced cancer? These data show that naloxegol is frequently added to an existing laxative treatment in patients with OIC (48.4 to 75.9% of patients) with cancer related pain. A greater relief of constipation was seen following combination treatment with naloxegol and a second laxative. The safety profile seen during combined use was comparable to that of naloxegol alone. Based on the data from these studies, safety in patients with cancer pain is no longer considered as missing information.
Diagnosis of liver cirrhosis as defined by Child-Pugh classes of B (moderate) or C (severe) or acute liver disease	The safety profile of naloxegol in this patient population was expected to be different because of the potential for decreased metabolism of naloxegol and enhanced CNS penetration of naloxegol due to potential disruption of the blood-brain barrier.	Yes
Patients with creatinine clearance < 30 mL/min	Patients with this degree of renal impairment were excluded because of potential accumulationof naloxegol that could change the safety profile.	Yes

Criteria	Reason for exclusion	Is it considered to be included as missing information?
Any condition that may have affected the permeability of the blood-brain barrier, eg, multiple sclerosis, recent brain injury, Alzheimer's disease, and uncontrolled epilepsy.	Patients were excluded from the clinical trials in order to avoid factors that may confound a complete understanding of the safety and efficacy of naloxegol. Naloxegol may cross the blood-brain-barrier in patients with these conditions and interfere with the analgesic effect of the opiate or cause opioid withdrawal.	No. Rationale: It is known that patientswith these conditions are at increased risk for opioid withdrawal and reversal of analgesia because naloxegol can enter the CNS. In the EU SmPC insection 4.4 Special warnings and special precautions for use it notes that 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 or reversal of analgesia.Thus, although the safety profile of this population may be different to that of the general target population it is not relevant or warranted to consider this population as missing information and to further evaluatethe safety profile.
Patients who are at increased risk for ventricular arrhythmia, including those that have a prior history of serious ventricular arrhythmia, family history of sudden cardiac death, family history of long QT syndrome, havea recent history of myocardial infarction within 6 months before randomization or who have overt cardiovascular disease	The safety of naloxegol in these patients was unknown. Cardiovascular effects were noted in the dog telemetry study and another member of the same drug class as naloxegol had a post-marketing safety signal of myocardial infarction. As a consequence, patients with overt cardiac disease could be more susceptible to serious cardiovascular adverse reactions.	Yes.
Pregnancy or lactation	Patients who were pregnant or lactating were excluded from the clinical trials due to safety reasons. The blood-brain barrier in humans is not fully developed until at least 6 months of age postpartum so there is a theoretical potential for provoking opioid withdrawal in the foetus or the nursing infant who is not older than 6 months of age with use of an opioid receptor antagonist in the mother, who is concurrently using an opioid.	Yes

Criteria	Reason for exclusion	Is it considered to be included as missing information?
Strong inhibitors of cytochromeP450 3A4 (CYP3A4) and P-glycoprotein (PGP) are prohibited	These drugs were prohibited because of safety. These inhibitors have the potential to increase the blood levels of naloxegol and the risk for its toxicity.	No. Rationale: Naloxegol is a substrate of CYP3A4 enzyme and a substrate of P-gp transporter. 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 section 5.2 EU SmPC Pharmacokinetic properties). It is therefore not relevant to include use with strong CYP3A4 inhibitors or P-gp as missing information. The starting dose of naloxegol should be 12.5 mg oncedaily when co-administered with moderate CYP3A4 inhibitors or dual Pgp/moderate CYP3A4 inhibitors (see sections 4.2 Posology and method of administration, 4.5 Interaction with other medicinal products andother forms of interaction and 5.2 Pharmacokinetic properties). After 168,554 patient- years of exposure in marketed use, there have been 4 cases of drug interactions reported that involve CYP3A4. Three interactions involved moderate inhibitors and one interaction involved phenytoin, a strong CYP3A4 inducer. The result of the phenytoin interaction was not reported as a decreased effect of naloxegol, but a reduced serum phenytoin level. Therefore, although there is evidence of a different safety profile when givenwith moderate CYP3A4 inhibitorsthere is little evidence of a significant clinical impact and thepotential risk is managed effectively through the product labeling.

2.4.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, and those caused by prolonged or cumulative exposure.

2.4.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 7: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the pre-authorisation clinical development programme
Breast feeding women	
Patient with relevant comorbidities:	
• Patients with hepatic impairment (Child-Pugh Class A and B)	• 16 patients (single-dose)
• Patients with renal impairment < 60ml/min	• 37 patients (9.9 patient-years)
• Patients with cardiovascular impairment	
• Immunocompromised patients	• The remaining 3 patient groups were not included in the pre-authorisation clinical development programme
• Patients with a disease severity different from inclusion criteria in clinical trials	
Patients with relevant different ethnic origin:	
• Not allowed to ask	• 1 patient (0.1 patient-years)
• White	• 1199 patients (488.7 patient-years)
• Black or African American	• 267 patients (120.8 patient-years)
• Asian	• 11 patients (5.2 patient-years)
• Native Hawaiian or other Pacific Islander	• 1 patient (0.2 patient-years)
• American Indian or Alaska native	• 7 patients (3.4 patient-years)
• Other	• 11 patients (5.8 patient-years)
Subpopulations carrying relevant genetic polymorphisms	Not included in the pre-authorisation clinical development programme

2.5 PART II: Module SV – Post-authorisation experience

2.5.1 Method used to calculate exposure

The post-marketing patient exposure data presented is estimated based on naloxegol's monthly actual ex-factory sales volume from each local marketing company. These data represent all naloxegol formulations delivered to various distribution channels (for example wholesalers, pharmacies, etc) worldwide. The database has the ability to pull data for complete months only and is limited to sales data only.

The sales volume is provided as the number of tablets distributed. The estimated post-marketing patient exposure data for the reporting period is an approximation based on the assumption that each patient took 1 tablet of naloxegol a day. Therefore, a patient-year worth of exposure is calculated by multiplying number of tablets per day by 365 days per patient year.

The current methodology does not distinguish between sales that are related to initial prescriptions versus those related to repeat prescriptions. Therefore, it is not possible to estimate the number of patients exposed to naloxegol. More detailed patient-level data (e.g. gender, ethnicity, age category, off-label use, specific populations etc) are not available.

2.5.2 Exposure

The cumulative global post-marketing patient exposure to naloxegol, since launch to 15 September 2021, has been estimated to be approximately 352,855 patient-years.

Table 8: Estimated Cumulative Exposure by Region

Region	**Patient-years**
Europe	89,128
North America	263,727
Total	**352,855**

Patient-years in this table have been rounded to the nearest whole number; therefore, the total may be greater or lower than the estimate given above.

Table 9: Estimated Cumulative Exposure by Dose

Naloxegol dose	Patient-years
12.5 mg	56,729
25 mg	296,126
Total	**352,855**

Patient-years in this table have been rounded to the nearest whole number; therefore, the total may be greater or lower than the estimate given above.

2.6 PART II: Module SVI – Additional EU requirements for the safety specification

2.6.1 Potential for misuse for illegal purposes

Based on the totality of non-clinical and clinical abuse potential data, it is concluded that naloxegol does not have abuse or dependence potential.

Pharmacologically, as a μ-opioid receptor antagonist, naloxegol is devoid of μ-opioid receptor partial agonist activity and does not have affinity for other receptors that are known to mediate the actions of a substance of abuse.

Non-clinical data strongly suggest that naloxegol is unlikely to be abused in man.

2.7 PART II: Module SVII – Identified and potential risks

2.7.1 Identification of safety concerns in the initial RMP submission

The safety concerns presented in the first approved EU RMP for naloxegol (RMP version 1.0) are listed in Table 10.

Table 10: Summary of safety concerns in the initial EU RMP

Important identified risks	Clinically important GI AEs Opioid Withdrawal Syndrome Interactions with drugs modulating CYP3A4and P-gp activities
Important potential risks	GI perforation Haemodynamic changes potentially leading to serious CV events (including effects on bloodpressure and syncope) Off-label use Interference with opioid mediated analgesia
Important missing information	Efficacy/safety in methadone treated patients Efficacy/safety in cancer pain population Efficacy/safety in high risk CV patients Efficacy/safety beyond 1 year of exposure Efficacy/safety in patients > 75 years of age Efficacy/safety in patients with severe renal impairment Efficacy/safety in hepatic impairment Efficacy/safety in non-Caucasian and non-African Black patients Efficacy/safety in paediatric populations Efficacy/safety in pregnancy and lactaction

AE Adverse event; CNS Central nervous system; GI gastrointestinal.

2.7.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Risks not considered important for inclusion in the list of safety concerns in the RMP are summarised in Table 11.

Table 11: Risks not considered important for inclusion in list of safety concerns

Justification for non-inclusion	MedDRA PT (frequency)
Risks with minimal clinical impact on patients (in relation to the severity of the indication treated)	Diarrhoea (very common) Nasopharyngitis (common) Headache (common) Flatulence (common) Nausea (common) Vomiting (common) Hyperhidrosis (common)
Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated	

2.7.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk: Opioid withdrawal syndrome

Opioid withdrawal syndrome is a listed ADR and is described in Section 4.8 Undesirable effects of the naloxegol CDS (Appendix 1). Case reports of OWS have been reported in the naloxegol clinical programme according to the Diagnostic and Statistical Manual of Mental Disorders [DSM]-5 definition. OWS 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. OWS typically develops within minutes to several days following administration of an opioid antagonist. The FDA definition of opioid withdrawal includes ≥1 non-GI symptoms in addition to having ≥3 OWS signs/symptoms with onset on the same day. According to the CDS, 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 of these reports were observed shortly after initial administration with the medicinal product and symptoms were mild or moderate in intensity.

In clinical trials opioid drug withdrawal in the absence of risk factors identified for opioid withdrawal (disrupted blood-brain barrier or overdose) was reported in < 1% of patients. About 12 % of the cases in the naloxegol safety database were considered serious. As of 15-Sep-2021, a review of the cumulative data in the naloxegol safety database does not change the current understanding of this topic.

Risk-benefit impact: When an opioid withdrawal occurs following naloxegol use, the increase in pain as well as other symptoms related to the withdrawal create a need to stop naloxegol.

Important Identified Risk: Clinically important gastrointestinal (GI) events

In clinical trials, all patients recovered from the clinically important GI events and no patient died. Reports of severe abdominal pain and/or severe diarrhoea have been observed in clinical trials with the 25 mg dose of naloxegol, typically occurring shortly after initiation of treatment. As a review of the naloxegol safety database, the majority of GI AEs reported were non-serious. A few cases of intestinal perforation reported occurred in a patient with peritoneal metastases which is a contraindication in the naloxegol SmPC.

Risk-benefit impact: Clinically important GI events can result in hospitalisation. Diarrhoea or vomiting can be serious if they aggravate pre-existing medical conditions such as renal insufficiency, hypotension or hypokalaemia. It is important that GI events are appropriately managed with naloxegol withdrawal.

Important Identified Risk: Gastrointestinal perforation

There were no reports of GI perforation in any of the Phase II/III studies. In addition, in the Phase III studies, all GI SAEs were adjudicated by an independent external adjudication committee to determine the potential for meeting the criteria for a bowel perforation event. All of the adjudicated events in naloxegol-treated patients were 'not related' to bowel perforation, according to the adjudication committee. Several reports of GI perforation have been received in the post marketing setting, a few of which have resulted in fatal outcomes in patients who were at risk for GI perforation. Many of these patients had known risk factors for GI perforation. As patients at risk of gastrointestinal perforation were excluded from clinical trials the role of naloxegol in contribution of these events cannot be excluded.

Risk-benefit impact: GI perforation is a surgical and life-threatening emergency and is generally associated with substantial morbidity as well as a high frequency (approximately 20 to 40%) of mortality (Azer 2009), being further associated with septic shock and multi-organ failure.

Although the precise nature of the GI perforation with naloxegol is unclear due to the small number of cases observed, the severity and potential implications of the condition in general impact the risk benefit balance of naloxegol.

Important Identified Risk: Interactions with drugs modulating CYP3A4 and P-gp activities

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

Risk-benefit impact: Impact is that naloxegol may require cessation of therapy and the OIC may recur.

Important Potential Risk: Haemodynamic changes potentially leading to serious cardiovascular events (including effects on blood pressure and syncope)

The overall incidence of adjudicated major adverse cardiovascular events (MACE) was low and similar across treatment groups both in the placebo-controlled studies and in the randomised, long-term safety study. The incidence of MACE adjudicated by the CV-EAC as meeting formal diagnostic criteria was 0.6% (9/700 patients) for placebo or UC versus 0.4% (5/1386 patients) for naloxegol.

Case reports of cardiovascular events have been noted in clinical studies and post marketing experience. The serious cardiovascular events reported were hypertension, hypotension, cerebrovascular accident, myocardial infarction, syncope and dyspnoea. More than half of these cases were reported as serious with several resulting in a fatal outcome. A causal association between naloxegol and serious CV events could not be established based on review of cases from clinical trials and post-marketing setting.

Risk-benefit impact: Serious cardiovascular events require intervention and possible hospitalisation. If not adequately managed these events can result in disability or even death.

Important Potential Risk: Interference with opioid mediated analgesia

All of the pain events in clinical studies were non-serious. Most patients recover from the pain event. In some cases, the patients recover during treatment with naloxegol; some patients recover after the naloxegol is discontinued. It is unlikely that the patients who recovered during treatment in the clinical trials were experiencing pain due to naloxegol's peripheral antagonism of opioid analgesia. Most patients who have opioid withdrawal induced by naloxegol do not have reversal of analgesia or decreased opioid effect suggesting that the patients are experiencing peripheral opioid withdrawal.

A review of the naloxegol drug safety database identified few cases of events of increased pain or decreased opioid efficacy in the absence of the opioid withdrawal syndrome. The majority of reported pain events were non-serious.

Post-hoc analysis and spontaneous reports suggest that naloxegol may rarely contribute to increased pain in some patients in the absence of the opioid withdrawal syndrome. In general, events such as increased pain are not associated with appreciable morbidity or mortality. Most cases were mild to moderate in intensity. A review of spontaneous reports where an outcome is provided indicate that generally naloxegol is discontinued and the patient recovers.

Risk-benefit impact: Impact is that naloxegol may require cessation of therapy and the OIC may recur.

Missing information: Use in high risk CV patients

There is insufficient information to determine if the safety profile in this population/utilisation is different to that of the general target population however due to medical judgement there is a concern that these patients may be at risk because of the preclinical findings in the dog and the fact that in some studies the incidence of cardiovascular events such as hypotension, hypertension, syncope, malignant hypertension and accelerated hypertension were higher than seen with usual care or a placebo.

Risk-benefit impact: The impact on individual patients is unknown due to there being insufficient data for analysis in high risk CV patients.

Missing information: Safety beyond one year of exposure

There is very little experience in patients exposed to naloxegol for longer than 1 year. As of 15-Sep-2021, there were only a few cases identified with use >1 year and the reports were all non-serious. No controlled study has been conducted.

It is unknown how long naloxegol will continue to work or if there are risks associated with use greater than 1 year.

Risk-benefit impact: The impact on individual patients is unknown due to there being insufficient data for analysis in patients who have used naloxegol for longer than one year.

Missing information: Use in methadone-treated patients

Patients receiving methadone for pain relief were included in clinical trials and had more frequent side effects affecting the gut (such as abdominal pain and diarrhoea) than patients not receiving methadone. Symptoms suggestive of opioid withdrawal were 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 Moventig should be used with caution in these patients. Patients who experience severe side effects affecting the gut may have the dose lowered to 12.5 mg.

Risk-benefit impact: The impact on individual patients is unknown due to there being insufficient data for analysis in methadone-treated patients.

Missing information: Use in pregnancy and lactation

Patients who were pregnant or lactating were excluded from the clinical trials due to safety reasons. The blood-brain barrier in humans is not fully developed until at least 6 months of age postpartum so there is a theoretical potential for provoking opioid withdrawal in the foetus or the nursing infant who is not older than 6 months of age with use of an opioid receptor antagonist in the mother, who is concurrently using an opioid.

Risk-benefit impact: The impact on individual patients is unknown due to there being insufficient data for analysis in use in pregnancy and lactation.

Missing information: Use in patients over 75 years of age

There is a small effect of age on the pharmacokinetics of naloxegol (approximately 0.7% increase in AUC for every year increase in age). No dose adjustment 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.

Risk-benefit impact: The impact on individual patients is unknown due to there being insufficient data for analysis in patients over 75 years of age.

Missing information: Use in patients with severe renal impairment

Patients with severe renal impairment were excluded from clinical trials because of potential accumulation of naloxegol that could change the safety profile. There is limited data available to confirm if the safety profile in this patient population is different to that of the general target population.

Risk-benefit impact: The impact on individual patients is unknown due to there being insufficient data for analysis in patients with severe renal impairment.

Missing information: Use in patients with severe hepatic impairment

This patient population was excluded from clinical trials as the safety profile of naloxegol was expected to be different because of the potential for decreased metabolism of naloxegol and enhanced CNS penetration of naloxegol due to

potential disruption of the blood-brain barrier. There is insufficient data for analysis to confirm if the safety profile is different in this patient population.

Risk-benefit impact: The impact on individual patients is unknown due to there being insufficient data for analysis in patients with severe hepatic impairment.

2.7.2 New safety concerns and reclassification with a submission of an updated RMP

Efficacy/safety in cancer pain population, previously categorized as a missing information in the EU RMP version 7.2 has been removed from the list of safety concerns based on the data from three non-interventional observational studies (KYONAL,NACASY, MovE). These data show that naloxegol is frequently added to an existing laxative treatment in patients with OIC (48.4 to 75.9% of patients) with cancer related pain. A greater relief of constipation was seen following combination treatment with naloxegol and a second laxative. The safety profile seen during combined use was comparable to that of naloxegol alone. Thus, safety in patients with cancer pain is no longer considered as missing information.

2.7.3 Details of important identified risks, important potential risks and missing information

2.7.3.1 Presentation of important identified risks

The important identified risks of opioid withdrawal syndrome, clinically important GI events, gastrointestinal perforation and interactions with drugs modulating CYP3A4 and P-gp activities are summarised in Table 12, Table 13, Table 14 and Table 15 respectively.

2.7.3.1.1 Opioid Withdrawal Syndrome

Information concerning the risk of opioid withdrawal syndrome are summarised in Table 12.

Table 12.Important Identified Risk – Opioid withdrawal syndrome

Important Identified Risk	Opioid withdrawal syndrome
Potential mechanism	Opioid receptors are distributed throughout the entire body, including in many locations outside the CNS. While this remains an area of evolving understanding, it is known that opioid receptors are present in the peripheral nervous system and also have a broad visceral distribution (Vadivelu et al 2011, Peng et al 2012). The intended mechanism of action for naloxegol is preferential antagonism of opioids at their receptors in the enteric plexi. The efficacy and GI AEs observed directly after initial naloxegol administration is likely related to localised gastrointestinal reversal of chronic, constipating opioid effects (i.e., reversal of impaired GI motility and decreased intestinal fluid absorption). Data from both animal studies and human studies support the involvement of peripheral opioid receptors in analgesia, especially in the presence of inflammation. (Sehgal et al 2011). The concept of central opioid withdrawal syndrome is more widely recognised in the literature than a peripherally-mediated syndrome. Central opioid withdrawal is characterised inthe DSM-5 as a constellation of clinically important symptoms occurring together in time and also temporally related to either cessation of opioid use orthe use of an opioid antagonist drug. Indeed, the clinical use of peripherally selective opioid antagonists to treat opioid-induced constipation is relatively recent and has been limited, to date, to small and well-circumscribed populations.
Evidence source(s) and strength of evidence	In clinical trials the opioid withdrawal syndrome was characterised as a syndrome resembling central opioid withdrawal and occurred uncommonly (≥1/1000, <1/100) in patients. The syndrome was more frequent in the naloxegol group than in the placebo or usual standard care group and there is aplausible mechanism of action for naloxegol to lead to this risk.
Characterisation of therisk	Opioid withdrawal syndrome is a listed ADR and is described in Section 4.8 Undesirable effects of the naloxegol CDS (Appendix 1). Case reports of OWS have been reported in the naloxegol clinical programme according to the Diagnostic and Statistical Manual of Mental Disorders [DSM]-5 definition. OWS 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. OWS typically develops within minutes to several days following administration of an opioid antagonist. The FDA definition of opioid withdrawal includes ≥1 non-GI symptoms in addition to having ≥3 OWS signs/symptoms with onset on the same day. According to the CDS, 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 of these reports were observed shortly after initial administration with the medicinal product and symptoms were mild or moderate in intensity. In clinical trials opioid drug withdrawal in the absence of risk factors identified for opioid withdrawal (disrupted blood-brain barrier or overdose) was reported in < 1% of patients. As of 15-Sep-2021, a review of the cumulative data in the naloxegol safety database does not change the current understanding of this topic.

Important Identified Risk	Opioid withdrawal syndrome
Risk factors and riskgroups	Risk factors for opioid withdrawal include use of methadone, an opioid dailydose ≥200 meu and a BMI ≥ 30 kg/m^2. Patients with any one of these risks experience opioid withdrawal at a much higher rate. There have been a few reports of the opioid drug withdrawal syndrome in patients concomitantly treated with other narcotic antagonists. The dose of naloxegol may also be a risk factor since it may be seen with overdoses in the absence of a blood-brain barrier disruption. However, review of the naloxegol safety database suggests that the opioid withdrawal occurs generally in the absence of these risk factors. Approximately 90% of all cases reported as opioid drug withdrawal codes (PTs withdrawal syndrome and drug withdrawal syndrome) did not include a specific pain event. Although most reports provide limited information, about 2% of the cases are reported to have a condition associated with disruption of the blood-brain barrier.
Preventability	The SmPC includes a number of warnings to reduce the occurrence of the opioid withdrawal syndrome. Section 4.4 **Special warnings and precautionsfor use** warns about an increased risk of opioid withdrawal or reversal of opioid analgesia in patients with conditions that disrupt the blood-brain barrierand provides some examples of these conditions. Section 4.9 of the SmPC reminds prescribers to be alert to symptoms of withdrawal syndrome if the patient takes an overdose of naloxegol.
Impact on the risk-benefitbalance of the product	When an opioid withdrawal occurs following naloxegol use, the increase in pain as well as other symptoms related to the withdrawal, create a need to stopnaloxegol.
Public health impact	As the impact is to the treated population only there is no public health impact.

2.7.3.1.2 Clinically important gastrointestinal events

Information concerning the risk of clinically important gastrointestinal events are summarised in Table 13.

Table 13: Important Identified Risk - Clinically important gastrointestinal (GI) events

Important Identified Risk	Clinically important gastrointestinal (GI) events
Potential mechanisms	Mu-opioid receptors have a multitude of physiologic effects on the bowel that increase the likelihood of constipation, including increased absorption of fluid, decreased propulsive peristalsis, and increased contraction of sphincters. The blockade of these receptors by naloxegol decreases opioid stimulation of receptors, which decreases the physiologic sequelae of opioids on the bowel that lead to constipation. These pharmacologic actions can occasionally be exaggerated in some individuals producing serious diarrhoea, vomiting or abdominal pain.
Evidence source(s) and strength of evidence	In the Phase III confirmatory studies (12 weeks), the frequency of patients with GI SAEs was low, with no imbalance between naloxegol (0.3%) and placebo (0.2%). However, the frequency of patients with SAEs was greater with naloxegol (3.9%) than with placebo (1.4%). There was a higher incidence of severe and/or SAEs of abdominal pain in patients taking the 25 mg dose compared to placebo (5.6% for naloxegol 25 mg vs. 0.9% placebo) and diarrhoea (1.6% for naloxegol 25 mg vs. 1.1% for placebo).
Characterisation of the risk	In these trials, all patients recovered from the clinically important GI events and no patient died. Reports of severe abdominal pain and/or severe diarrhoea have been observed in clinical trials with the 25 mg dose of naloxegol, typically occurring shortly after initiation of treatment. As a review of the naloxegol safety database, the majority of GI AEs reported were non-serious. A few cases of intestinal perforation reported occurred in a patient with peritoneal metastases which is a contraindication in the naloxegol SmPC.
Risk factors and risk groups	Risk factors for non-serious gastrointestinal events are the use of methadone, an opioid daily dose ≥200 meu, a BMI ≥ 30 kg/m^2 and the dose of naloxegol. It is likely that these are also risk factors for clinically important GI events. Potential risk factors seen in serious post-marketing cases of abdominal pain included opioid withdrawal in 15% of cases, a history of GI disease in 30% of cases and the remainder had no reported risk factor. One serious case was associated with a drug interaction between diltiazem and naloxegol.
Preventability	Clinically important GI effects can be avoided by not administering naloxegol to patients at high risk for GI obstruction or perforation (see Section 4.3 Contraindications, Section 4.4 Special warnings and precautions for use and Section 4.2 Posology and method of administration of the SmPC). The severity of the gastrointestinal event can be reduced by following the instruction in the SmPC to reduce the dose to 12.5 mg and for the patient to promptly report severe, persistent or worsening abdominal pain or diarrhoea to their doctor.

Important Identified Risk	Clinically important gastrointestinal (GI) events
Impact on the risk-benefit balance of the product	Clinically important GI events can result in hospitalisation. Diarrhoea or vomiting can be serious if they aggravate pre-existing medical conditions such as renal insufficiency, hypotension or hypokalaemia. It is important that GI events are appropriately managed with naloxegol withdrawal.
Public health impact	As the impact is to the treated population only there is no public health impact.

2.7.3.1.3 Gastrointestinal perforation

Information concerning the risk of gastrointestinal perforation are summarised in Table 14.

Table 14: Important Identified Risk - Gastrointestinal (GI) perforation

Important Identified Risk	Gastrointestinal (GI) perforation
Potential mechanisms	With respect to an OIC population both spontaneous colonic perforation and stercoral colonic perforation are relevant. Spontaneous colonic perforation, as the name implies, occurs in the absence of overt risk factors and, while rare, is likely often misdiagnosed. Stercoral perforation refers to rupture of the GI tract by its internal contents, most typically by hardened faeces (i.e., faecaloma) associated with chronic constipation and in the absence of other risk factors. Also considered a rare (but possibly under diagnosed) disorder, it is believed to be caused by either intrinsic gut hypomotility or drug-induced hypomotility. It is reported more commonly in the distal colon, where a confluence of factors (less water content, more precarious blood supply and narrowness of the local bowel) conspire to increase susceptibility to mechanical insult (Haddad et al 2005). The final common denominator regarding the pathophysiology of stercoral perforation is thought to be an ischaemic pressure necrosis with associated inflammatory change (Dubinsky 1996).
Evidence source(s) and strength of evidence	Clinical studies and post-marketed use. GI perforations have been observed with naloxegol use, two of which have been fatal. A search of the FDA Adverse Event Reporting System (April 24, 2008 through October 13, 2009) identified 6 cases of GI perforation for patients receiving methylnaltrexone. In addition, three AstraZeneca initiated observational studies utilizing US, UK and German electronic healthcare databases reported incidence rates of GI tract perforations among adult patients (≥18 years of age) with chronic continuous opioid use and a US-based administrative claims study reported an incidence rate of 0.007 per patient year. This rate increased to 0.541 per patient-year when patients with a prior history of GI tract perforations were included. Using the UK CPRD-HES linkage, incidence of GI tract perforation was 0.0001 per patient year. This rate increased to 0.0003 when including indicators of prior GI tract perforations. Using the German IMS Disease Analyzer database, an incidence rate of 0.001 per patient year was reported. Allowing for prior history of GI tract perforation, it increased the rate to 0.503 per patient year.

Important Identified Risk	Gastrointestinal (GI) perforation
Characterisation of the risk	There were no reports of GI perforation in any of the Phase II/III studies. In addition, in the Phase III studies, all GI SAEs were adjudicated by an independent external adjudication committee to determine the potential for meeting the criteria for a bowel perforation event. All of the adjudicated events in naloxegol-treated patients were 'not related' to bowel perforation, according to the adjudication committee. Several reports of GI perforation have been received in the post marketing setting, a few of which have resulted in fatal outcomes in patients who were at risk for GI perforation. Many of these patients had known risk factors for GI perforation. As patients at risk of gastrointestinal perforation were excluded from clinical trials the role of naloxegol in contribution of these events cannotbe excluded.
Risk factors and risk groups	The most notable risk factor is a medical history including GI events, this is reflected in the naloxegol SmPC where use in contraindicated in patients with known or GI obstruction or in patients at increased risk of recurrent obstruction. In addition, Section 4.4 of the SmPC recommends caution with regards to the use of naloxegol 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) Some cancer patients may be at risk for GI perforation for multiple reasons. Of particular note are anti-angiogenic agents, particularly bevacizumab, a monoclonal antibody targeting the vascular endothelial growth factor (VEGF). This risk seems to be higher in patients with advanced ovarian cancer. At highest risk are patients with pre-existing GI tract tumour involvement (obstruction or bowel wall thickening) and those who have undergone recent surgery or received prior pelvic radiation. Bowel perforation occurred at a median of 71 days after initiation of bevacizumab therapy and 14 days after the last dose of drug. Patients with advanced or recurrent malignancies known to be associated with higher rates of malignant bowel obstruction, such as advanced or recurrent ovarian, colon, or small bowel cancer, may also be at increased risk.

Important Identified Risk	Gastrointestinal (GI) perforation
Preventability	The SmPC contraindicates the use of naloxegol when the patients are at risk for GI perforation. **(section 4.3 Contraindications)** It also mitigates the risk if it does occur by warning the patients to contact their doctor if they develop any signs of perforation. **Section 4.4, Special warnings and special precautions for use** in the naloxegol SmPC states that cases of gastrointestinal perforation have been reported in post-marketing setting, including fatal cases when naloxegol was used in patients who were at an increased risk of gastrointestinal (GI) perforation. Naloxegol must not be used in patients with known or suspected gastrointestinal obstruction or in patients at increased risk of recurrent obstruction, or in patients with underlying cancer who are heightened risk of GI perforation. 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, taking into account the overall benefit-risk profile for a given patient. Patients should be advised to discontinue therapy with naloxegol and promptly notify their physician if they develop unusually severe or persistent abdominal pain. Section 4.8 lists gastrointestinal perforation as an adverse reaction which occurs at 'unknown' frequency.
Impact on the risk-benefit balance of the product	GI perforation is a surgical and life-threatening emergency and is generally associated with substantial morbidity as well as a high frequency (approximately 20 to 40%) of mortality (Azer 2009), being further associated with septic shock and multi-organ failure. Although the precise nature of the GI perforation with naloxegol is unclear due to the small number of cases observed, the severity and potential implications of the condition in general impact the risk benefit balance of naloxegol.
Public health impact	As the impact is to the treated population only, there is no public health impact.

2.7.3.1.4 Interactions with drugs modulating CYP3A4 and P-gp activities

Information concerning the risk of interactions with drugs modulating CYP3A4 andP-gp activities are summarised in Table 15.

Table 15: Important Identified Risk – Interactions with drugs modulating CYP3A4 and P-gp activities

Important Identified Risk	Interactions with drugs modulating CYP3A4 and P-gp activities
Potential mechanisms	The metabolic stability of naloxegol was studied in vitro in the presence of individual human cytochrome P450 (CYP) enzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) expressed in bacterial membranes. Naloxegol was metabolised primarily by CYP3A4 and not by the other CYP enzymes tested. This was further confirmed in human liver microsomes. Naloxegol is not a substrate for organic anion transporter protein (OATP) 1B1, OATP1B3, or breast cancer resistance protein (BCRP) but is a p-glycoprotein (P-gp) substrate in vitro. As renal elimination is a minor route of clearance for naloxegol, the potential for naloxegol to act as a substrate of organic cation transporter (OCT) 2, organic anion transporter (OAT) 1, or OAT3 was not examined.

Evidence source(s) and strength of evidence	<u>Interaction with strong CYP3A4 inhibitors</u> 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 Cmax (90% CI: 8.1-11.3), compared to when naloxegol was administered alone. Therefore, concomitant use with strong CYP3A4 inhibitors is contraindicated. 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. <u>Interaction with moderate CYP3A4 inhibitors</u> In an open-label, non-randomised, 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 is recommended when co-administered with diltiazem or other moderate CYP3A4 inhibitors. <u>Interaction with strong CYP3A4 inducers</u> 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, coadministration of rifampin and naloxegol resulted in a 89% (90% CI: 88%-90%) decrease in naloxegol AUC and a 76% decrease in naloxegol Cmax (90% CI: 69%-80%), compared to when naloxegol was administered alone. Therefore, Moventig is not recommended in patients who are taking strong CYP3A4 inducers. <u>Interaction with P-gp inhibitors</u> A double-blind, randomised, 2-part, crossover, single-center study was conducted to evaluate the effect of quinidine on the PK 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 Cmax (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 increase 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.
Characterisation of the risk	Naloxegol is a sensitive substrate of CYP3A4 enzyme and a substrate of P-gp transporter. Co-administration of dual P-gp/ strong or moderate CYP3A4 inhibitors, or strong CYP3A4 inhibitors significantly increases naloxegol plasma concentrations. Conversely, co-administration of a strong CYP3A4 inducer results in decreased plasma concentration.

Risk factors and risk groups	Based on its in vitro enzyme and transporter induction and inhibition profile, naloxegol is not likely to perpetrate pharmacokinetic-based drug-drug interactions. Naloxegol is metabolised mainly by CYP3A4 and is a substrate of P-gp. Drugs that modulate CYP3A4 and P-gp activities are likely to influence the PK of naloxegol.
Preventability	The SmPC contains a number of warnings regarding the concomitant use of naloxegol and drugs modulating CYP3A4 and P-gp activities. Section 4.2 of the SmPC: 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. Section 4.3 of the SmPC: 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) Section 4.4 of SmPC: Naloxegol is not recommended in patients who are taking strong CYP3A4 inducers (e.g. carbamazepine, rifampin, St. John's wort) Section 4.5 of the SmPC reiterates the warnings in section 4.2, 4.3 and 4.4 of the SmPC and details the evidence source of this risk as summarized above.
Impact on the risk-benefit balance of the product	Impact is that naloxegol may require cessation of therapy and the OIC may recur.
Public health impact	As the impact is to the treated population only, there is no public health impact.

2.7.3.2 Presentation of important potential risks

The important potential risks of haemodynamic changes potentially leading to serious cardiovascular events (including effects on blood pressure and syncope) and interference with opioid mediated analgesia are summarised in Table 16 and Table 17.

2.7.3.2.1 Haemodynamic changes potentially leading to serious cardiovascular events (including effects on blood pressure and syncope)

Information concerning the risk of haemodynamic changes potentially leading to serious cardiovascular events (including effects on blood pressure and syncope) are summarised in Table 16.

Table 16: Important Potential Risk - Haemodynamic changes potentially leading to serious cardiovascular events (including effects on blood pressure and syncope)

Important Potential Risk	Haemodynamic changes potentially leading to serious cardiovascular events (including effects on blood pressure and syncope)
Potential mechanisms	Cardiovascular effects were observed in the dog telemetry study and were limited to moderate decreases in arterial blood pressure, left ventricular systolic pressure and indices of cardiac contractility. The NOAEL for these effects was at 5mg/kg and an exposure (maximum concentration [Cmax]) comparable to human exposure at the MRHD. The mechanism for this pre-clinical finding is currently unknown. Of note, the effects of naloxegol on contractility parameters in canine ventricular myocytes were investigated at 0.1, 1, 10 and 100 μmol/L. Draft data show that naloxegol had no effect on cardiac myocyte contractility at any of the concentrations tested, suggesting this finding might not be due to direct effects of naloxegol on the cardiac contractility.
Evidence source(s) and strength of evidence	Non-clinical studies, clinical studies and potential class effect. <u>Syncope</u> Across the Phase III studies during the treatment periods (N=2134), 6 patients reported an AE of syncope, and 1 patient reported pre-syncope. All 7 patients were randomised to naloxegol with 2/7 patients on the 12.5 mg dose and 5/7 patients on the 25 mg dose. The single report of pre-syncope occurred on Day 55 in conjunction with an AE of "infection." <u>Serious CV SAEs</u> A total of 68 unique events of CV SAEs and potentially relevant CV AEs (23 AEs in 18/700 patients who received placebo or usual-care (UC) and 45 AEs in 36/1386 patients who received naloxegol) for 54 unique patients were submitted to the Cardiovascular-Event Adjudication Committee (CV-EAC) for adjudication. Of these, 10 events in 9 patients were adjudicated as MACE. Major adverse cardiovascular events were identified as possible risks due to a potential CV safety signal (myocardial ischaemia) reported from a long-term safety study of alvimopan, another peripherally acting opioid antagonist. However, no biologically plausible mechanism for increased cardiovascular toxicity has been identified.
Characterisation of the risk	The overall incidence of adjudicated MACE was low and similar across treatment groups both in the placebo-controlled studies and in the randomised, long-term safety study. The incidence of MACE adjudicated by the CV-EAC as meeting formal diagnostic criteria was 0.6% (9/700 patients) for placebo or UC versus 0.4% (5/1386 patients) for naloxegol.

Important Potential Risk	Haemodynamic changes potentially leading to serious cardiovascular events (including effects on blood pressure and syncope)
Important Potential Risk	Haemodynamic changes potentially leading to serious cardiovascular events (including effects on blood pressure and syncope) Case reports of cardiovascular events have been noted in clinical studies and post marketing experience. The serious cardiovascular events reported were hypertension, hypotension, cerebrovascular accident, myocardial infarction, syncope and dyspnoea. More than half of these cases were reported as serious with several resulting in a fatal outcome. A causal association between naloxegol and serious CV events could not be established based on review of cases from clinical trials and post-marketing setting.
Risk factors and risk groups	Based on a post-hoc assessment of CV risk, two thirds of the patients had at least 1 CV risk factor and one third of the patients had CV disease, diabetes, or ≥2 CV risk factors consistent with the minimally restrictive nature of the eligibility criteria. Patients with a history of hypertension may be at increased risk for hypertension with minimal difference compared to placebo. A history of syncope or use of concomitant antihypertensives or low baseline blood pressure appears to increase the risk of syncope. In a post-hoc analysis,1% patients taking an opioid dose ≥200 meu with naloxegol 25 mg experienced malignant hypertension or presyncope. There is also evidence from a post-hoc analysis that the risk for adverse cardiovascular events may also be higher in patients with a BMI ≥30 kg/m2. In a post-hoc analysis of the 12-week pool, naloxegol 25-mg patients with a BMI≥ 30 kg/m2 (N=226 on naloxegol 25 mg/ N=216 on placebo) had the following frequencies of CV AEs: syncope and blood pressure increased (both 0.4% on naloxegol 25 mg vs 0% on placebo), hypertension (1.8% vs 0.5%, respectively), hypotension (0.9% vs 0.5 %, respectively), and malignant hypertension, orthostatic hypotension, and accelerated hypertension (all 0.4% vs 0%, respectively).
Preventability	There is no information in the SmPC of naloxegol to prevent or minimize this potential risk.
Impact on the risk-benefit balance of the product	Serious cardiovascular events require intervention and possible hospitalisation. If not adequately managed these events can result in disability or even death.
Public health impact	As the impact is to the treated population only, there is no public health impact.

2.7.3.2.2 Pain due to reduced efficacy of the opioid in the absence of the opioid withdrawal syndrome

Information concerning the risk of pain due to reduced efficacy of the opioid in the absence of the opioid withdrawal syndrome are summarised in Table 17.

Table 17: Important Potential Risk – Interference with opioid mediated analgesia

Important Potential Risk	Interference with opioid mediated analgesia
Potential mechanisms	As a μ-opioid antagonist, PEGylated naloxegol has been designed to not enter the CNS at the dose range anticipated for clinical use. Theoretically, disruption of the Blood-Brain Barrier (BBB) could allow access of naloxegol into the CNS, with interference with opioid mediated analgesia resulting in increased pain. Some patients appear to be dependent on peripheral opioid receptors for analgesia and blockade of these receptors decreases the opioid analgesic effect. Evidence suggests that the peripheral opioid receptors play a particularly important role in the presence of inflammation.
Evidence source(s) and strength of evidence	In an invitro pre-clinical study, the dose required to reduce analgesia was 2.4 times greater than dose required to reduce the constipation. Clinical trials show a higher incidence of pain events in naloxegol group vs standard of care group. In the Phase III long-term study (52 weeks), the frequency of pain-related AEs (N=481 on naloxegol 25 mg/ N=240 on UC) in naloxegol 25 mg compared to UC were as follows: back pain (8.9% on naloxegol 25 mg vs 8.8% on UC), pain in extremity (3.5% vs. 3.3%, respectively), fibromyalgia (2.1% vs 1.3%, respectively), osteoarthritis (1.5% vs 1.3%, respectively), neuralgia (1.0% vs 0.8%, respectively), and cervical neuritis, drug effect decreased, and cervical radiculitis (all 0.2% vs 0%, respectively). In clinical trials opioid withdrawal occurred uncommonly in the absence of a blood-brain-barrier disruption; peripheral decreases in analgesic effect may be occurring in a few post-marketing cases since opioid withdrawal is not reported nor are any symptoms.
Characterisation of the risk	All of the pain events in clinical studies were non-serious. Most patients recover from the pain event. In some cases, the patients recover during treatment with naloxegol; some patients recover after the naloxegol is discontinued. It is unlikely that the patients who recovered during treatment in the clinical trials were experiencing pain due to naloxegol's peripheral antagonism of opioid analgesia. Most patients who have opioid withdrawal induced by naloxegol do not have reversal of analgesia or decreased opioid effect suggesting that the patients are experiencing peripheral opioid withdrawal. A review of the naloxegol drug safety database identified few cases of events of increased pain or decreased opioid efficacy in the absence of the opioid withdrawal syndrome. The majority of reported pain events were non-serious. Post-hoc analysis and spontaneous reports suggest that naloxegol may rarely contribute to increased pain in some patients in the absence of the opioid withdrawal syndrome. In general, events such as increased pain are not associated with appreciable morbidity or mortality. Most cases were mild to moderate in intensity. A review of spontaneous reports where an outcome is provided indicate that generally naloxegol is discontinued and the patient recovers.

Risk factors and risk groups	There is evidence that the incidence of opioid drug withdrawal and possibly decreased opioid effect may be higher with the use of methadone than other opioid agonists, but this comparison has not been directly made. The incidence of withdrawal with methadone has only been compared to placebo in post hoc analyses. In a post-hoc analysis of the 12-week pool, naloxegol 25-mg patients receiving methadone therapy as their primary therapy for chronic pain conditions had low frequencies of pain-related AEs (event included if frequency was numerically higher in naloxegol 25 mg than placebo), such as back pain (3.7 % on naloxegol 25 mg vs 3.4% on placebo) and peripheral neuropathy (3.7% vs 0%, respectively). There is also evidence from post-hoc analysis that the risk of opioid withdrawal and possibly decreased analgesic efficacy may be higher when an opioid dose is ≥200 meu and the patient has BMI ≥30 kg/m2. The incidence of pain events also appears to be higher in patients using naloxegol long-term versus 12 weeks. Spontaneous reports suggest that reduced opioid efficacy occurs with all opioids. There is insufficient information to determine whether the severity is greater with methadone.
Preventability	The SmPC notes that reversal of analgesic effect may occur in 2 situations in the presence of a condition associated with a disrupted blood-brain barrier (**Section 4.4, Special warnings and special precautions for use)** or overdose **(Section 9)**.
Impact on the risk-benefit balance of the product	Impact is that naloxegol may require cessation of therapy and the OIC may recur.
Public health impact	As the impact is to the treated population only, there is no public health impact.

2.7.3.3 Presentation of missing information

The missing information of use in high risk CV patients, safety beyond one year of exposure, use in methadone-treated patients, use in pregnancy and lactation, use in patients over 75 years of age, use in patients with severe renal impairment and use in patients with severe hepatic impairment are summarised in Table 18, Table 19, Table 20, Table 21, Table 22, Table 23 and Table 24 respectively.

2.7.3.3.1 Use in high risk CV patients

Information concerning the missing information of use in high risk CV patients are summarised in Table 18.

Table 18: Missing information - Use in high risk CV patients

Missing information	Use in high risk CV patients
Evidence source	There is insufficient information to determine if the safety profile in this population/utilisation is different to that of the general target population however due to medical judgement there is a concern that these patients may be at risk because of the preclinical findings in the dog and the fact that in some studies the incidence of cardiovascular events such as hypotension, hypertension, syncope, malignant hypertension and accelerated hypertension were higher than seen with usual care or a placebo.
Population in need of further characterisation	Data for use in high risk CV patients is being collected in PASS study D382000008.

2.7.3.3.2 Safety beyond one year of exposure

Information concerning the missing information of safety beyond one year of exposure are summarised in Table 19.

Table 19: Missing information - Safety beyond one year of exposure

Missing information	Safety beyond one year of exposure
Evidence source	There is very little experience in patients exposed to naloxegol for longer than 1 year. As of 15-Sep-2021, there were only a few cases identified with use >1 year and the reports were all non-serious. No controlled study has been conducted. It is unknown how long naloxegol will continue to work or if there are risks associated with use greater than 1 year.
Population in need of further characterisation	Data for use beyond 1 year is being collected in PASS study D382000008.

2.7.3.3.3 Use in methadone-treated patients

Information concerning the missing information of use in methadone-treated patients are summarised in Table 20.

Table 20: Missing information – Use in methadone-treated patients

Missing information	Use in methadone-treated patients
Evidence source	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.

2.7.3.3.4 Use in pregnancy and lactation

Information concerning the missing information of use in pregnancy and lactationare summarised in Table 21.

Table 21: Missing information – Use in pregnancy and lactation

Missing information	Use in pregnancy and lactation
Evidence source	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. Lactation 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 nursing mothers is not recommended.

2.7.3.3.5 Use in patients over 75 years of age

Information concerning the missing information of use in patients over 75 years of age are summarised in Table 22.

Table 22: Missing information – Use in patients over 75 years of age

Missing information	Use in patients over 75 years of age
Evidence source	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 from 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.

2.7.3.3.6 Use in patients with severe renal impairment

Information concerning the missing information of use in patients with severe renal impairment are summarised in Table 23.

Table 23: Missing information – Use in patients with severe renal impairment

Missing information	Use in patients with severe renal impairment
Evidence source	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 hemodialysis was similar to healthy volunteers with normal renal function.

2.7.3.3.7 Use in patients with severe hepatic impairment

Information concerning the missing information of use in patients with severe hepatic impairment are summarised in Table 24.

Table 24: Missing information – Use in patients with severe hepatic impairment

Missing information	Use in patients with severe hepatic impairment
Evidence source	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 nalogexol was not evaluated. Use in patients with severe hepatic impairment is not recommended.

2.8 PART II: Module SVIII – Summary of safety concerns

2.8.1 Summary of the safety concerns

A summary of the safety concerns for naloxegol is presented in Table 25.

Table 25: Summary of safety concerns

Important identified risks	Opioid Withdrawal Syndrome Clinically Important Gastrointestinal Events Gastrointestinal perforation Interactions with drugs modulating CYP3A4 and P-gp activities
Important potential risks	Haemodynamic changes potentially leading to serious cardiovascular events (including effects on blood pressure and syncope) Interference with opioid mediated analgesia
Missing information	Use in high risk CV patients Safety beyond one year of exposure Use in methadone-treated patients Use in pregnancy and lactation Use in patients over 75 years of age Use in patients with severe renal impairment Use in patients with severe hepatic impairment

3. PART III: PHARMACOVIGILANCE PLAN

3.1 Routine pharmacovigilance activities

Specific adverse reaction follow-up questionnaire for gastrointestinal perforation

This form should provide KKI with the temporal relationship to naloxegol, the concomitant medications and risk factors for gastrointestinal perforation and how the diagnosis was established.

Other forms of routine pharmacovigilance activities for safety concerns

Non-applicable

3.2 Additional pharmacovigilance activities

Table 26: Summary details of study D3820R00008

Study short name and title:	**D3820R00008**: United States Post-Marketing Observational Cardiovascular Safety Study in Patients Taking Naloxegol.
Rationale and study objectives:	The primary objective of this study is to assess the overall risk of major adverse Cardio Vascular (CV) events (ie, CV death, non-fatal myocardial infarction, non-fatal stroke and MACE) among naloxegol treated patients compared to that among patients on prescription non-peripherally acting μ-opioid antagonist OIC treatment.
Study design:	A retrospective new-user cohort design is used to assess the risk of MACE in persons receiving naloxegol or comparison medication (lubiprostone or linaclotide).
Study Population:	Patients 18 years of age or older without a prior diagnosis of cancer and who receive chronic opioid treatment. Subjects will be identified from 2015–2020, using data from HealthCore (HC) and the US Veterans Health Administration (VHA).
Milestones:	Interim data: Annual reports are provided. Final data: 4Q 2023

3.3 Summary table of additional pharmacovigilance activities

Table 27: Ongoing and planned additional pharmacovigilance activities

Study/Status	Summary of objectives	Safety concerns addressed	Milestones (for EMA)	Due dates (for EMA)
Category 3 - Required additional pharmacovigilance activities				
D3820R00008 United States Post-Marketing Observational Cardiovascular Safety Study in Patients taking naloxegol (Retrospective, new-user cohort design)	To assess the overall risk of Major Adverse Cardiovascular Events (MACE) among naloxegol treated patients compared to that among patients on non-PAMORA prescription OIC treatments. Oral non-naloxegol PAMORAs will be included as these agents become available on the market.	Haemodynamic changes potentially leading to serious cardiovascular events (including effects on blood pressure and syncope) Use in high risk CV patients Safety beyond one year of exposure	**Interim Data** **Final data**	Annual reports. 4Q 2023

Opioid Induced Constipation PK: Pharmacokinetics, PAMORA Peripherally Acting mu-Opioid Receptor Antagonist PASS: Post-Authorisation Safety Study.

4. PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

No post-authorisation efficacy studies are ongoing or planned at this point in time.

5. PART V: RISK MINIMISATION MEASURES

5.1 Routine Risk minimisation measures

Table 28: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Opioid withdrawal syndrome	**Routine risk communication**: SmPC Section 4.4, Special warnings and special precautions for use states this identified event is more likely to occur in patients with disrupted blood-brain barrier PIL Section,4 Possible side effects- up to 1% of patients experience opioid withdrawal and describes the side effects of opioid withdrawal **Routine risk minimisation activities recommending specific clinical measures to address the risk**: SmPC Section 4.4 recommends caution when prescribing naloxegol to patients with clinically important disruptions to the blood-brain barrier, taking into account their individual benefit-risk balance with observation for potential CNS effects, such as symptoms of opioid withdrawal. SmPC Section 4.9, Overdose recommends that patients who have an overdose of naloxegol be monitored closely for potential evidence of opioid withdrawal symptoms. PIL Section 2, Take special care before taking naloxegol if the natural protective barrier between the blood vessels in the head and in the brain is damaged, such as after a recent brain injury, or if you have a disease of the central nervous system like multiple sclerosis or Alzheimer's Disease

Table 28: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Clinically Important Gastrointestinal Events	**Routine risk communication**: SmPC Section 4.4, Special warnings and special precautions for use explains that severe diarrhoea and/or abdominal pain have occurred, and the events are seen with the 25 mg dose SmPC Section 4.8, Undesirable effects-abdominal pain and diarrhoea are very common, and vomiting is common (PIL: Section 4, Possible side effects- stomach pain and diarrhoea may occur in more than 10% of people and vomiting in up to 10% **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.4 Special warnings and special precautions for use advises patients to promptly report severe, persistent or worsening GI symptoms to their physician. Consideration may be given to lowering the dose to 12.5 mg in patients experiencing severe GI events. PIL Section 2, Take special care before taking naloxegol if you have you currently have severe or persistent stomach pain and/or diarrhoea or are taking methadone; if: you develop severe or persistent stomach pain and/or diarrhoea contact your physician PIL Section 4, Possible side effects- Tell your doctor immediately if you have severe or persistent stomach pain and or diarrhoea.
GI perforation	**Routine risk communication**: SmPC Section 4.3, Contraindications informs prescribers when naloxegol use is not recommended or contraindicated because of a high risk of GI perforation SmPC Section 4.8, Undesirable effects PIL Section 4, Possible side effects – gastrointestinal perforation (a hole developing in the bowel wall) **Routine risk minimisation activities recommending specific clinical measures to address the risk**: SmPC Section 4.4 Special warnings and special precautions for use recommends caution regarding the use of naloxegol in patients with any condition which might result in impaired integrity of the gastrointestinal tract wall. These patients are advised to discontinue therapy with naloxegol and promptly notify their physician if they develop unusually severe or persistent abdominal pain. PIL Section 2, What you need to know before you take naloxegol: Do not take naloxegol if your bowels are, or may be, blocked (obstructed) or you have been warned that your bowels are at risk of becoming blocked. PIL Section 2, Take special care with Naloxegol- before taking naloxegol if you have severe 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 condition that might damage the wall of your bowel talk to your doctor.

Table 28: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Interactions with drugs modulating CYP3A4 and P-gp activities	**Routine risk communications:** SmPC Section 4.2 states that no dose adjustment is necessary for concomitant use of naloxegol with dual Pgp/weak CYP3A4 inhibitors SmPC Section 4.3 states that concomitant use with dual Pgp/strong CYP3A4 inhibitors can significantly increase exposure to naloxegol and is contraindicated. SmPC Section 4.4 reinforces the warnings included in Section 4.2 In addition it states that grapefruit has been classified as a CYP3A4 inhibitor. No data is available of the concomitant use of naloxegol and grapefruit, so it is recommended that concomitant use is avoided and considered only in consultation with a healthcare provider. SmPC Section 4.5 includes a summary of the data available relating to this risk including that grapefruit has been classified as a potent CYP3A4 inhibitor when consumed in large quantities. No data is available of the concomitant use of naloxegol and grapefruit, so it is recommended that concomitant use is avoided and considered only in consultation with a healthcare provider. PIL Section 2 warns that naloxegol should not be taken if the patient is taking other medications such as ketoconazole or itraconazole (to treat fungal infections), clarithromycin or telithromycin (antibiotics) or ritonavir, indinavir or saquinavir (to treat HIV). It also warns that patients should not drink large amounts of grapefruit juice whilst taking naloxegol. **Routine risk minimisation activities recommending specific clinical measures to address the risk**: SmPC Section 4.2 details recommends patients concomitantly taking moderate CYP3A4 inhibitors or dual Pgp/moderate CYP3A4 inhibitors should start on a dose of 12.5 mg, which can be increased to 25 mg if this is well tolerate by the patient. SmPC Section 4.5 reinforces the warning in Section 4.2 that the starting dose of patients concomitantly taking moderate CYP3A4 inhibitors is 12.5 mg, and that this can be increased if well tolerated. PIL Section 3 warns that the patient's doctor may tell them to take a lower dose of 12.5 mg if they take diltiazem or verapamil (for high blood pressure or angina).
Haemodynamic changes potentially leading to serious cardiovascular events (including effects on blood pressure and syncope)	**Routine risk communication**: None **Routine risk minimisation activities recommending specific clinical measures to address the risk**: None

Table 28: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Interference with opioid mediated analgesia	**Routine risk communication**: SmPC Section 4.4, Special warnings and special precautions for use- there may be increased risk of reversal of analgesia if patient has a disrupted blood-brain barrier **Routine risk minimisation activities recommending specific clinical measures to address the risk**: SmPC Section 4.4 recommends caution when prescribing naloxegol to patients with clinically important disruptions to the blood-brain barrier taking into account their individual benefit-risk balance with observation for potential CNS effects, such as symptoms of reversal of analgesia. SmPC Section 4.9, monitor closely for potential evidence of opioid reversal of central analgesic effect
Use in high risk CV patients	**Routine risk communication**: None **Routine risk minimisation activities recommending specific clinical measures to address the risk**: None
Safety beyond one year of exposure	**Routine risk communication**: None **Routine risk minimisation activities recommending specific clinical measures to address the risk**: None
Use in methadone-treated patients	**Routine risk communication**: SmPC Section 4.4: Concurrent methadone use PIL Section 2 states that patients should talk to their doctor, pharmacist or nurse before taking Moventig if they are taking methadone **Routine risk minimisation activities recommending specific clinical measures to address the risk**: None
Use in pregnancy and lactation	**Routine risk communication**: SmPC Section 4.6 states that there are limited data from the use of naloxegol in pregnant women, and that it is unknown whether naloxegol is excreted in human milk. PIL Section 2 states that Moventig is not recommended for use during pregnancy or during breast-feeding. **Routine risk minimisation activities recommending specific clinical measures to address the risk**: None

Table 28: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Use in patients over 75 years of age	**Routine risk communication**: SmPC Section 4.2 states that no dose adjustment is recommended based on age. **Routine risk minimisation activities recommending specific clinical measures to address the risk**: None
Use in patients with severe renal impairment	**Routine risk communication**: SmPC Section 4.2 PIL Section 3 states that the patient's doctor may advise a lower dose if the patient has kidney problems **Routine risk minimisation activities recommending specific clinical measures to address the risk**: SmPC Section 4.2 states that 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.
Use in patients with severe hepatic impairment	**Routine risk communication**: SmPC Section 4.2 states that use in patients with severe hepatic impairment is not recommended. SmPC Section 4.4 states that naloxegol has not been studied in patients with severe hepatic impairment and use of naloxegol is not recommended in such patients. **Routine risk minimisation activities recommending specific clinical measures to address the risk**: None

5.2 Additional risk minimisation measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

5.3 Summary of risk minimisation measures

Table 29: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Table 29:Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Opioid withdrawal syndrome	**Routine risk minimisation measures**: SmPC Section 4.8, Undesirable effects SmPC Section 4.4 recommends caution when prescribing naloxegol to patients with clinically important disruptions to the blood-brain barrier, taking into account their individual benefit-risk balance with observation for potential CNS effects, such as symptoms of opioid withdrawal. SmPC Section 4.5, concomitant use of other narcotic antagonists not recommended. SmPC Section 4.9, recommends that patients who have an overdose of naloxegol be monitored closely for potential evidence of opioid withdrawal symptoms. PIL Section 4: Possible side effect PIL Section 2, Take special care	**Additional pharmacovigilance activities** **None**
Clinically important gastrointestinal events	**Routine risk minimisation measures:** SmPC Section 4.8, Undesirable effects SmPC Section 4.4 advises patients to promptly report severe, persistent or worsening GI symptoms to their physician. Consideration may be given to lowering the dose to 12.5 mg in patients experiencing severe GI events. PIL Section 2, Take special care with naloxegol PIL Section 4, Possible side effects	**Additional pharmacovigilance activities**: **None**
GI perforation	**Routine risk minimisation measures:** SmPC Section 4.3, Contraindications Section 4.4, Special warnings and special precautions for use Section 4.8, Undesirable effects **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.3 states that naloxegol is contraindicated in patients with known or suspected GI obstruction and in patients at	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up questionnaire/ intake mechanism for post-marketing reports of GI perforation **Additional pharmacovigilance activities:** **None**

	increased risk of recurrent obstruction. In addition, naloxegol should not be used in patients with cancer pain who are at heightened risk of GI perforation**.** SmPC Section 4.4 recommends caution regarding the use of naloxegol in patients with any condition which might result in impaired integrity of the gastrointestinal tract wall. These patients are advised to discontinue therapy with naloxegol and promptly notify their physician if they develop unusually severe or persistent abdominal pain. PIL Section 2, What you need to know before you take naloxegol PIL Section 2, Take special care with Naloxegol PIL Section 4, Possible side effects **Other routine risk minimisation measures beyond the Product Information:** None	
Interactions with drugs modulating CYP3A4 and P-gp activities	**Routine risk communications:** SmPC Section 4.2 states that no dose adjustment is necessary for concomitant use of naloxegol with dual Pgp/weak CYP3A4 inhibitors SmPC Section 4.3 states that concomitant use with dual Pgp/strong CYP3A4 inhibitors can significantly increase exposure to naloxegol and is contraindicated. SmPC Section 4.4 reinforces the warnings included in Section 4.2 In addition it states that grapefruit has been classified as a CYP3A4 inhibitor. No data is available of the concomitant use of naloxegol and grapefruit, so it is recommended that concomitant use is avoided and considered only in consultation with a healthcare provider. SmPC Section 4.5 includes a summary of the data available relating to this risk including that grapefruit has been classified as a potent CYP3A4 inhibitor when consumed in large quantities. No data is available of the concomitant use of naloxegol and grapefruit, so it is recommended that concomitant use is avoided and considered only in consultation with a healthcare provider.	**Additional pharmacovigilance activities**: **None**

	PIL Section 2 warns that naloxegol should not be taken if the patient is taking other medications such as ketoconazole or itraconazole (to treat fungal infections), clarithromycin or telithromycin (antibiotics) or ritonavir, indinavir or saquinavir (to treat HIV). It also warns that patients should not drink large amounts of grapefruit juice whilst taking naloxegol. **Routine risk minimisation activities recommending specific clinical measures to address the risk**: SmPC Section 4.2 details recommends patients concomitantly taking moderate CYP3A4 inhibitors or dual Pgp/moderate CYP3A4 inhibitors should start on a dose of 12.5 mg, which can be increased to 25 mg if this is well tolerate by the patient. SmPC Section 4.5 reinforces the warning in Section 4.2 that the starting dose of patients concomitantly taking moderate CYP3A4 inhibitors is 12.5 mg, and that this can be increased if well tolerated. PIL Section 3 warns that the patient's doctor may tell them to take a lower dose of 12.5 mg if they take diltiazem or verapamil (for high blood pressure or angina).	
Haemodynamic changes potentially leading to serious cardiovascular events (including effects on blood pressure and syncope)	**Routine risk minimisation measures:** None	**Additional pharmacovigilance activities** **Study D3820R00008** Naloxegol US PMR CV Safety
Interference with opioid mediated analgesia	**Routine risk minimisation measures:** SmPC Section 4.4 recommends caution when prescribing naloxegol to patients with clinically important disruptions to the blood-brain barrier taking into account their individual benefit-risk balance with observation for potential CNS effects, such as symptoms of reversal of analgesia. SmPC Section 4.9, monitor closely for potential evidence of opioid withdrawal symptoms or reversal of central analgesic effect	**Additional pharmacovigilance activities** **None**

Safety beyond one year of exposure	**Routine risk minimisation measures:** None	**Additional pharmacovigilance activities** **Study D3820R00008** Naloxegol US PMR CV Safety
Use in high risk CV patients	**Routine risk minimisation measures:** None	**Additional pharmacovigilance activities** **Study D3820R00008** Naloxegol US PMR CV Safety
Use in methadone-treated patients	**Routine risk minimisation measures:** SmPC Section 4.4: Concurrent methadone use PIL Section 2 states that patients should talk to their doctor, pharmacist or nurse before taking Moventig if they are taking methadone	**Additional pharmacovigilance activities** **None**
Use in pregnancy and lactation	**Routine risk minimisation measures:** SmPC Section 4.6 states that there are limited data from the use of naloxegol in pregnant women, and that it is unknown whether naloxegol is excreted in human milk. PIL Section 2 states that Moventig is not recommended for use during pregnancy or during breast-feeding.	**Additional pharmacovigilance activities** **None**
Use in patients over 75 years of age	**Routine risk minimisation measures:** SmPC Section 4.2 states that no dose adjustment is recommended based on age.	**Additional pharmacovigilance activities** **None**

Use in patients with severe renal impairment	**Routine risk minimisation measures:** SmPC Section 4.2 states that 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. PIL Section 3 states that the patient's doctor may advise a lower dose if the patient has kidney problems	**Additional pharmacovigilance activities** **None**
Use in patients with severe hepatic impairment	**Routine risk minimisation measures:** SmPC Section 4.2 states that use in patients with severe hepatic impairment is not recommended. SmPC Section 4.4 states that naloxegol has not been studied in patients with severe hepatic impairment and use of naloxegol is not recommended in such patients.	**Additional pharmacovigilance activities** **None**

6. PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR MOVENTIG

This is a summary of the risk management plan (RMP) for Moventig. The RMP details important risks of Moventig, how these risks can be minimised, and how more information will be obtained about Moventig's risks and uncertainties (missing information).

Moventig's Summary of Product Characteristics (SmPC), (which is the prescribing information) and its Package Leaflet (PL) give essential information to healthcare professionals and patients on how Moventig should be used.

Important new concerns or changes to the current ones will be included in updates of the Moventig RMP.

6.1 The medicine and what it is used for

Moventig is authorised for the treatment of Opioid-Induced Constipation (OIC) in adult patients who have had an inadequate response to laxative(s) (see SmPC for the full indication). It contains naloxegol as the active substance and it is given by the oral route.

Further information about the evaluation of Moventig's benefits can be found in Moventig's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/moventig

6.2 Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Moventig, together with measures to minimise such risks and the proposed studies for learning more about Moventig's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Moventig is not yet available, it is listed under 'missing information' below.

6.2.1 List of important risks and missing information

Important risks of Moventig are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Moventig. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

A summary of the important risks and missing information for Moventig is provided in Table 30.

Table 30:List of important risks and missing information

Important identified risks	Opioid Withdrawal Syndrome Clinically Important Gastrointestinal Events Gastrointestinal perforation Interactions with drugs modulating CYP3A4 and P-gp activities
Important potential risks	Haemodynamic changes potentially leading to serious cardiovascular events (including effects on blood pressure and syncope) Interference with opioid mediated analgesia
Missing information	Use in high risk CV patients Safety beyond one year of exposure Use in methadone-treated patients Use in pregnancy and lactation Use in patients over 75 years of age Use in patients with severe renal impairment Use in patients with severe hepatic impairment

6.2.2 Summary of important risks

Further information about the important risks and missing information for Moventig is provided in Table 31.

Table 31:Summary of important risks for Moventig

Important identified risk – Opioid Withdrawal Syndrome	
Evidence for linking the risk to the medicine	Clinical trial data and frequent spontaneous reports
Risk factors and risk groups	Use of methadone, an opioid daily dose ≥200 meu and a BMI ≥ 30 kg/m^2 and the dose of Moventig, conditions associated with BBB disruption, overdose, concomitant use of other opioid antagonists and cardiovascular morbidity. Approximately 90% of all cases reported as opioid drug withdrawal codes (PTs withdrawal syndrome and drug withdrawal syndrome) did not include a specific pain event were missing
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC Section 4.8, Undesirable effects SmPC Section 4.4 recommends caution when prescribing Moventig to patients with clinically important disruptions to the blood-brain barrier, taking into account their individual benefit-risk balance with observation for potential CNS effects, such as symptoms of opioid withdrawal. SmPC Section 4.5, concomitant use of other narcotic antagonists not recommended. SmPC Section 4.9, recommends that patients who have an overdose of Moventig be monitored closely for potential evidence of opioid withdrawal symptoms. PIL Section 4: Possible side effect PIL Section 2, Take special care
Additional pharmacovigilance activities	**None**
Important identified risk – Clinically Important Gastrointestinal Events	
Evidence for linking the risk to the medicine	Clinical trial data
Risk factors and risk groups	Use of methadone, an opioid daily dose ≥200 meu and a BMI ≥ 30 kg/m^2, the dose of Moventig, concomitant medical conditions that could be aggravated by diarrhoea or vomiting
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC Section 4.8, Undesirable effects SmPC Section 4.4 advises patients to promptly report severe, persistent or worsening GI symptoms to their physician. Consideration may be given to lowering the dose to 12.5 mg in patients experiencing severe GI events. PIL Section 2, Take special care with naloxegol PIL Section 4, Possible side effects
Additional pharmacovigilance activities	**None**
Important identified risk - Gastrointestinal perforation	

Evidence for linking the risk to the medicine	Post marketing experience with peripheral opioid antagonists including Moventig and three KKI-sponsored observational studies utilising US, UK and German electronic healthcare databases
Risk factors and risk groups	The presence of any medical conditions that may be associated with localised or diffuse reduction of structural integrity in the wall of the GI tract (underlying malignancies of gastrointestinal tract or peritoneum, recurrent or advanced ovarian cancer, vascular endothelial growth factor (VEGF) inhibitor treatment, peptic ulcer, pseudo-obstruction, active or recurrent diverticulitis, Crohn's disease, history of GI obstruction
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC Section 4.3, Contraindications SmPC Section 4.4, Special warnings and special precautions for use <u>Routine risk minimisation activities recommending specific clinical measures to address the risk:</u> SmPC Section 4.3 states that Moventig is contraindicated in patients with known or suspected GI obstruction and in patients at increased risk of recurrent obstruction. In addition, Moventig should not be used in patients with cancer pain who are at heightened risk of GI perforation**.** SmPC Section 4.4 recommends caution regarding the use of Moventig in patients with any condition which might result in impaired integrity of the gastrointestinal tract wall. These patients are advised to discontinue therapy with Moventig and promptly notify their physician if they develop unusually severe or persistent abdominal pain. SmPC Section 4.8, Undesirable effects PIL Section 2, What you need to know before you take Moventig PIL Section 2, Take special care with Moventig PIL Section 4, Possible side effects
Additional pharmacovigilance activities	Targeted follow-up questionnaire/ intake mechanism for post-marketing reports of GI perforation
Important identified risk – Interactions with drugs modulating CYP3A4 and P-gp activities	
Evidence for linking the risk to the medicine	Non-clinical studies confirmed that naloxegol is metabolised mainly by CYP3A4 and is a substrate of P-gp. Drugs that modulate CYP3A4 and P-gp activities are likely to influence the pharmacokinetics of Moventig.
Risk factors and risk groups	Use of Moventig with medicines that are cleared from the body in the same way as Moventig may result in either an increase in Moventig levels in the blood, with possible increase in side effects, or a decrease of Moventig levels in the blood, with possible loss of effectiveness.
Risk minimisation measures	**Routine risk communications:** SmPC Section 4.2 states that no dose adjustment is necessary for concomitant use of Moventig with dual Pgp/weak CYP3A4 inhibitors SmPC Section 4.3 states that concomitant use with dual Pgp/strong CYP3A4 inhibitors can significantly increase exposure to naloxegol and is contraindicated. SmPC Section 4.4 reinforces the warnings included in Section 4.2 In addition it states that grapefruit has been classified as a CYP3A4 inhibitor. No data is available

	of the concomitant use of Moventig and grapefruit, so it is recommended that concomitant use is avoided and considered only in consultation with a healthcare provider. SmPC Section 4.5 includes a summary of the data available relating to this risk including that grapefruit has been classified as a potent CYP3A4 inhibitor when consumed in large quantities. No data is available of the concomitant use of Moventig and grapefruit, so it is recommended that concomitant use is avoided and considered only in consultation with a healthcare provider. PIL Section 2 warns that Moventig should not be taken if the patient is taking other medications such as ketoconazole or itraconazole (to treat fungal infections), clarithromycin or telithromycin (antibiotics) or ritonavir, indinavir or saquinavir (to treat HIV). It also warns that patients should not drink large amounts of grapefruit juice whilst taking Moventig. **Routine risk minimisation activities recommending specific clinical measures to address the risk**: SmPC Section 4.2 details recommends patients concomitantly taking moderate CYP3A4 inhibitors or dual Pgp/moderate CYP3A4 inhibitors should start on a dose of 12.5 mg, which can be increased to 25 mg if this is well tolerate by the patient. SmPC Section 4.5 reinforces the warning in Section 4.2 that the starting dose of patients concomitantly taking moderate CYP3A4 inhibitors is 12.5 mg, and that this can be increased if well tolerated. PIL Section 3 warns that the patient's doctor may tell them to take a lower dose of 12.5 mg if they take diltiazem or verapamil (for high blood pressure or angina).
Additional pharmacovigilance activities	**None**
Important potential risk – Haemodynamic changes potentially leading to serious cardiovascular events (including effects on blood pressure and syncope)	
Evidence for linking the risk to the medicine	Post-marketing experience with alvimopan,(another peripheral opioid receptor antagonist), preclinical evidence and clinical trials Serious CV SAEs A total of 68 unique events of CV SAEs and potentially relevant CV AEs (23 AEs in 18/700 patients who received placebo or UC and 45 AEs in 36/1386 patients who received Moventig) for 54 unique patients were submitted to the Cardiovascular-Event Adjudication Committee (CV-EAC) for adjudication. Of these, 10 events in 9 patients were adjudicated as MACE. Major adverse cardiovascular events were identified as possible risks due to a potential CV safety signal (myocardial ischaemia) reported from a long-term safety study of alvimopan, another peripherally acting opioid antagonist. However, no biologically plausible mechanism for increased cardiovascular toxicity has been identified.
Risk factors and risk groups	A post-hoc assessment of CV risk found two thirds of the patients had at least 1 CV risk factor and one third of the patients had CV disease, diabetes, or ≥2 CV risk factors, a history of cardiovascular disease or syncope, an opioid dose ≥200 meu and a BMI ≥ 30 kg/m2
Risk minimisation measures	None
Additional pharmacovigilance activities	**Study D3820R00008** Naloxegol US PMR CV Safety

Important potential risk – Interference with opioid mediated analgesia	
Evidence for linking the risk to the medicine	Indirect evidence from clinical trials showing higher incidence of pain events in Moventig group vs standard of care group. Increased pain events were not correlated with opioid withdrawal, or reversal of analgesia or decreased analgesic effect of the opioid. In an invitro pre-clinical study, the dose required to reduce analgesia was 2.4 x greater than dose required to reduce the constipation.
Risk factors and risk groups	Clinically important disruptions to the blood-brain barrier, overdose and potentially the same risk factors for the opioid withdrawal syndrome - use of methadone, an opioid daily dose ≥200 meu and a BMI ≥ 30 kg/m^2
Risk minimisation measures	Routine risk minimisation measures: Section 4.4 recommends caution when prescribing Moventig to patients with clinically important disruptions to the blood-brain barrier taking into account their individual benefit-risk balance with observation for potential CNS effects, such as symptoms of reversal of analgesia. Section 4.9, monitor closely for potential evidence of opioid withdrawal symptoms or reversal of central analgesic effect
Additional pharmacovigilance activities	**None**
Missing Information – Use in high risk CV patients	
Risk minimisation measures	Routine risk minimisation measures: None
Additional pharmacovigilance activities	**Study D3820R00008** Naloxegol US PMR CV Safety
Missing Information – Safety beyond one year of exposure	
Risk minimisation measures	Routine risk minimisation measures: None
Additional pharmacovigilance activities	**Study D3820R00008** Naloxegol US PMR CV Safety
Missing information – Use in methadone-treated patients	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4: Concurrent methadone use PIL Section 2 states that patients should talk to their doctor, pharmacist or nurse before taking Moventig if they are taking methadone
Additional pharmacovigilance activities	**None**
Missing information – Use in pregnancy and lactation	

Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.6 states that there are limited data from the use of Moventig in pregnant women, and that it is unknown whether Moventig is excreted in human milk. PIL Section 2 states that Moventig is not recommended for use during pregnancy or during breast-feeding.
Additional pharmacovigilance activities	**None**
Missing information – Use in patients over 75 years of age	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 states that no dose adjustment is recommended based on age
Additional pharmacovigilance activities	**None**
Missing information – Use in patients with severe renal impairment	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 states that the starting dose for patients with moderate or severe renal insufficiency is 12.5 mg. If side effects impacting tolerability occur, Moventig should be discontinued. The dose can be increased to 25 mg if 12.5 mg is well tolerated by the patient. PIL Section 3 states that the patient's doctor may advise a lower dose if the patient has kidney problems
Additional pharmacovigilance activities	**None**
Missing information – Use in patients with severe hepatic impairment	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 states that use in patients with severe hepatic impairment is not recommended. SmPC Section 4.4 states that Moventig has not been studied in patients with severe hepatic impairment and use of naloxegol is not recommended in such patients.
Additional pharmacovigilance activities	**None**

6.2.3 Post-authorisation development plan

6.2.3.1 Studies which are conditions of the marketing authorisation

There are no studies which conditions of the marketing authorisation or specific obligation of Moventig.

6.2.3.2 Other studies in post-authorisation development plan

Study short name and title:

D3820R00008: United States Post-Marketing Observational Cardiovascular Safety Study in Patients Taking Naloxegol.

Purpose of the study:
The purpose of the study is to collect data and assess rates regarding the overall risk of major adverse cardiovascular events in naloxegol-treated patients compared to patients on prescription non-peripherally acting μ-opioid antagonist OIC treatment.

Rationale and study objectives:

A retrospective new-user cohort design is used to assess the risk of MACE in persons receiving naloxegol or comparison medication (lubiprostone or linaclotide).

The primary objective of this study is to assess the overall risk of major adverse Cardiovascular (CV) events (ie, CV death, non-fatal myocardial infarction, non-fatal stroke and MACE) among naloxegol-treated patients compared to that among patients on prescription non-peripherally acting mu-opioid antagonist OIC treatment.

Patients 18 years of age or older without a prior diagnosis of cancer and who receive chronic opioid treatment. Subjects will be identified from 2015–2020, using data from HealthCore (HC) and the US Veterans Health Administration (VHA).

7. Annexes

Table 32:Index of Annexes

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Annex 4 – Specific adverse drug reaction follow-up forms

- *Gastrointestinal perforation*

Naloxegol ® Gastrointestinal perforation QUESTIONNAIRE

Please **check the appropriate Adverse Event/ Serious Adverse Event Box:** ☐

Stomach perforation ☐ *Small intestine perforation* ☐ *Large intestine perforation* ☐

Other GI perforation (_____)

Date:	**Reporter'sName:Reporter'sSpecialty:**
AENumber:	**Reporter'sAddress:** **PhoneNumber:**
Patient'sGender/Age/Height/Weight:	**INDICATIONforuseofNaloxegol®?** **Naloxegol®Dosage?**
Naloxegol®StartDate? **Naloxegol®StopDate?**	
Pleasecarefullydescribetheexactnatureofthiseventandhowitwasdiagnosed:	
Carefullydescribethetimecourseandoutcomeofthisevent,especiallywithrespecttotheadministrationofNaloxegol®:	
Pleasebrieflydescribeconcomitantmedication:	
Please provideallrecentandpastmedical/surgicalhistory:	
Canyousharethehigh-levelresultsofanyrecentdiagnostictests?Pleasebrieflydescribe:	
HasthispatienthadahistoryofgastrointestinalobstructionorknownperitonealadhesionspriortoNaloxegol®administration?IfYes,please providedetails.	
Please provideanyadditionalinformationthatyoufeelisinformative	

Return completed form to Kyowa Kirin International plc

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Annex 6 – Details of proposed additional risk minimisation activities (if applicable)

None.

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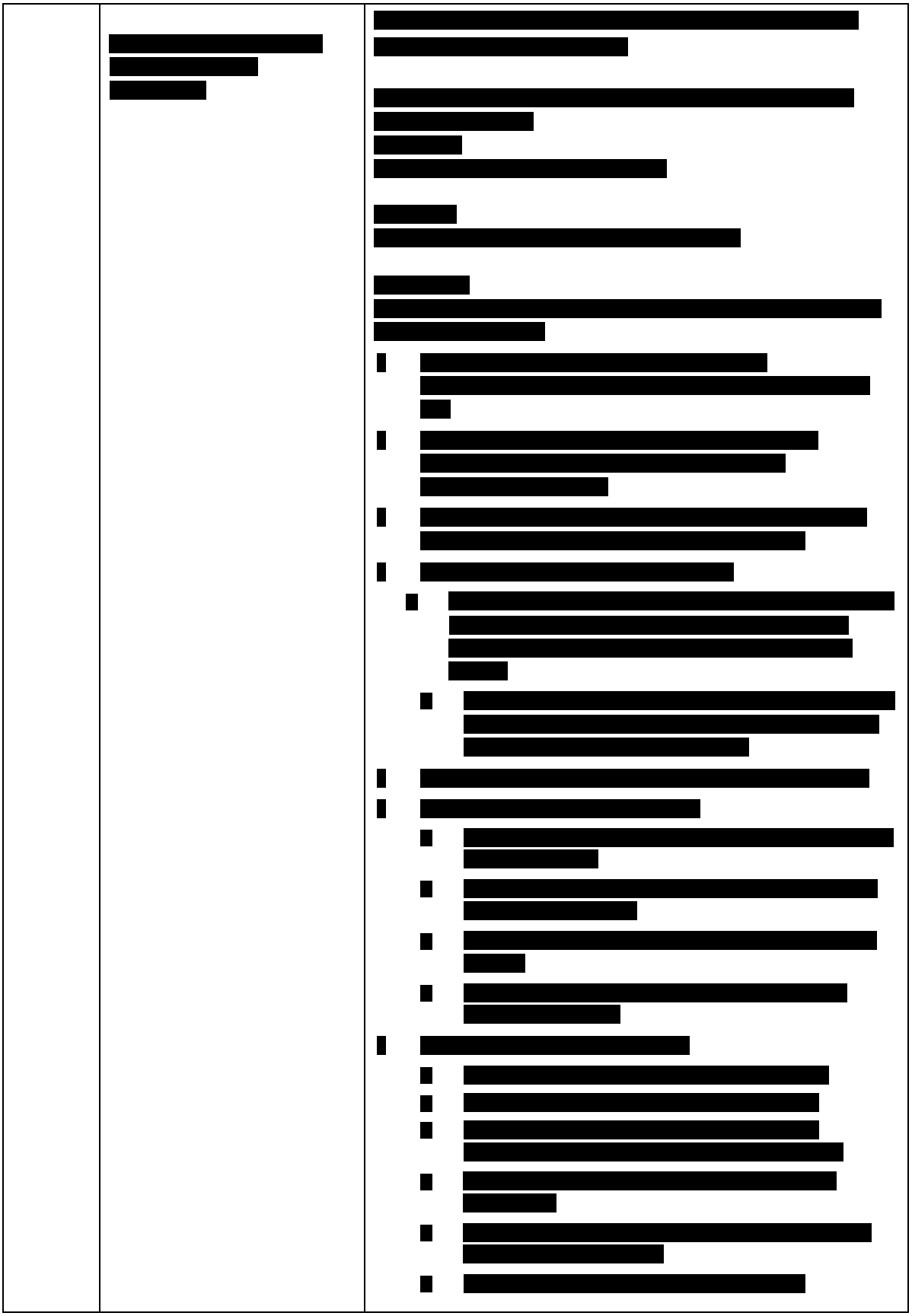

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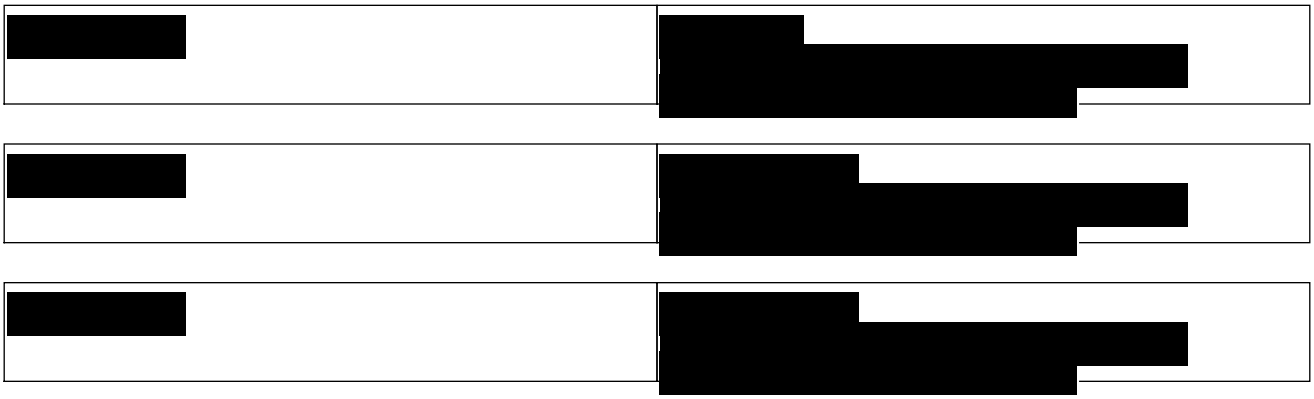

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