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EU RISK MANAGEMENT PLAN FOR MOVENTIG (NALOXEGOL)

RMP version to be assessed as part of this application:

RMP version number:	Version 10.0
Data lock point for this RMP: Date of final sign off: Rationale for submitting an updated RMP:	15 September 2023 30 October 2024 The RMP update is required as part of the Type-II variation Amendment of RMP following the completion of study D3820R00008 (United States Post-Marketing Observational Cardiovascular Safety Study in Patients Taking Naloxegol) to remove all the safety concerns.

Summary of significant changes in this RMP:

- Removal of all safety concerns

Other RMP versions under evaluation:	RMP version 9.0 was submitted to remove the study D3820R00008 and the safety concern "haemodynamic changes potentially leading to serious cardiovascular events (including effects on blood pressure and syncope)" from the list of important potential risks and "use in high risk CV Patients" from the list of missing information based on results of study D3820R00008. This RMP version 10.0 is submitted to remove all safety concerns from the RMP in line with recommendations from Assessment Report for the Post-Authorisation Measure MEA 006.14 – 006.15, Procedure number: EMA/PRAC/22513/2024, from 08 Feb 2024.

Details of currently approved RMP

Version number:	**8.2**
Approved with procedure:	EMEA/H/C/002810/II/0039

QPPV name: Dr. Fabian Heisig

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.

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
BBB	Blood brain barrier
CI	Confidence Interval
Cmax	Maximum concentration
CNS	Central Nervous System
CRC	Concurrent Reference Cohort
CV	Cardiovascular
CYP3A4	Cytochrome P450 3A4
DLP	Data Lock Point
EEA	European Economic Area
EMA	European Medicine Agency
EMEA	European Medicines Evaluation Agency
EPAR	European public assessment report
EU RMP	European Union Risk Management Plan
GI	Gastrointestinal
GVP	Good Pharmacovigilance Practices
hERG	Human either-a-go-go-related gene
INN	International Nonproprietary Names
MACE	Major adverse cardiovascular event
MRHD	Maximum Recommended Human Dose
NIC	Naloxegol Inception Cohort
NOAEL	No-Observed-Adverse-Effect-Level
NSAID	Non-steroidal anti-inflammatory drug
OIC	Opioid Induced Constipation
PAMORA	Peripherally-Acting Mu-Opioid Receptor Antagonist
PASS	Post-Authorization Safety Study
P-gp	P glycoprotein

Abbreviation	Explanation
PIP	Pediatric Investigation Plan
PK	Pharmacokinetic
PRAC	Pharmacovigilance Risk Assessment Committee
QPPV	Qualified Person for Pharmacovigilance (EU)
RMP	Risk Management Plan
RR	Relative Risk
SmPC	Summary of Product Characteristics (EU)
TK	Thymidine Kinase
UK	United Kingdom
US	United States

PART I: PRODUCT(S) OVERVIEW

Table 1: Product Overview

Active substance(s) (INN or common name)	Naloxegol
Pharmacotherapeutic group(s) (ATC Code)	A06AH03
Marketing Authorisation Holder	Grünenthal GmbH
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?	No

PART II: SAFETY SPECIFICATION

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

SI.1 Opioid-induced constipation (OIC)

SI.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 respect 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).

SI.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).

SI.1.3Demographics 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 2055 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.)

SI.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).

SI.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).

SI.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.

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

SII.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.

SII.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.

PART II: Module SIII: Clinical trial exposure

SIII.1 Summary of clinical trial exposure

Overall cumulative subject exposure is provided in Table 2, based on actual exposure data from completed interventional clinical trials. The completed studies are Phase I study D3820C00016, Phase IIb Study 07-IN-NX003 and Phase III Studies D3820C00004, D3820C00005, D3820C00006, D3820C00007 and 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 D3820C00006.

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 I study D3820C00016, Phase IIb Study 07-IN-NX003 and Phase III Studies D3820C00004, D3820C00005, D3820C00006, D3820C00007 and D3820C00008).

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)

Duration of exposure	Subjects n (%)
≥50 Weeks	245 (13.9)
≥ 52 Weeks	85 (4.8)
Total	**1,765**

Table 3: Cumulative exposure of 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	887
Total	**649**	**1,116**	**1,765**

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**

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

Part II: Module SIV - Populations not studied in clinical trials

SIV.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 treatment for cancer pain	Patients with cancer pain may be receiving treatment for 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 opioidinduced constipation in patients with cancer: KYONAL study. • Davies 2022. A prospective, real-world, multinationals 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? This data shows 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

Criteria	Reason for exclusion	Is it considered to be included as missing information?
		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 accumulation of 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, e.g., 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 patients with these conditions are at increased risk for opioid withdrawal and reversal of analgesia because naloxegol can enter the CNS. In the EU SmPC in section 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 evaluate the 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, have a 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.	No. Rationale: The United States PostMarketing Observational Cardiovascular (CV) Safety Study in Patients Taking Naloxegol (D3820R00008) was completed. Based on the results, there was no evidence of an increased risk of Major Adverse Cardiovascular Events (MACE) with naloxegol when compared to comparator treatment group.
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 cytochrome P450 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 Pgp 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 once daily when coadministered with moderate CYP3A4 inhibitors or dual P-gp/moderate CYP3A4 inhibitors (see sections 4.2 Posology and method of administration, 4.5 Interaction with other medicinal products and other 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 given with moderate CYP3A4 inhibitors, there is little evidence of a significant clinical impact and the potential risk is managed effectively through the product labeling.

SIV.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.

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

PART II: Module SV – Post-authorisation experience

SV.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.

SV.2 Exposure

The cumulative global post-marketing patient exposure to naloxegol, since launch to 15 September 2023, has been estimated to be approximately 500,900 patient-years.

Table 8: Estimated Cumulative Exposure by Region

Region	**Patient-years**
Europe	155,458
North America	345,442
Total	**500,900**

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	86,763
25 mg	414,137
Total	**500,900**

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.

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

SVI.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.

PART II: Module SVII – Identified and potential risks

SVII.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 CYP3A4 and P-gp activities
Important potential risks	GI perforation Haemodynamic changes potentially leading to serious CV events (including effects on blood pressure 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.

SVII.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 summarized in the Table 11:

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

Justification for non-inclusion	**List of risks/adverse drug reactions**
Risks with minimal clinical impact on patients (in relation to the severity of the indication treated)	Diarrhoea Nasopharyngitis Headache Flatulence

Justification for non-inclusion	List of risks/adverse drug reactions
	Nausea Vomiting Hyperhidrosis
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	
Known risks that require no further characterization and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting.	Clinically important GI AEs* Opioid Withdrawal Syndrome* Interactions with drugs modulating CYP3A4 and P-gp activities* GI perforation* Haemodynamic changes potentially leading to serious CV events (including effects on blood pressure and syncope) * Off-label use* Interference with opioid mediated analgesia*

* These risks were removed from the list of safety concerns in the context of the update of the RMP from Version 9.0 to 10.0.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Important identified and potential risks are those that may impact the product's benefit-risk assessment and/or may have a potential public health impact and that require either further characterization or evaluation or implementation of additional risk minimization activities to protect patients. No risk is currently meeting these criteria. Since none of the safety concerns (SC) necessitate additional risk minimization measures and additional pharmacovigilance activities in accordance with GVP Module V Revision 2, all safety concerns have been removed from the current RMP.

At this stage of the product life cycle, all known risks do not require further characterization and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting.

All risks named in the previous version are appropriately managed via routine risk minimization measures such as their description in the respective subsections of the summary of product characteristics (SmPCs) and Package Leaflet (PL).

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

The important potential risk of haemodynamic changes potentially leading to serious CV events (including effects on blood pressure and syncope) and missing information of efficacy/safety in

high risk CV have been excluded from the list of safety concerns in the EU RMP version 8.2. This decision is based on the findings of the post-marketing CV study D3820R00008, which indicates no evidence of an increased risk of Major Adverse Cardiovascular Events (MACE) with naloxegol compared to the comparator treatment group. This new information strengthens the cardiovascular safety profile for naloxegol. Consequently, haemodynamic changes potentially leading to serious CV events (including effects on blood pressure and syncope) are no longer deemed as an important potential risk and efficacy/safety in high-risk CV patients is no longer considered missing information.

Additionally, all remaining safety concerns have been removed from the list of safety concerns in line with the recommendations from Assessment Report for the Post-Authorisation Measure MEA 006.14 – 006.15, Procedure number: EMA/PRAC/22513/2024 and in accordance with GVP Module V Revision 2, as there is no additional pharmacovigilance activities and/or additional risk minimization measures.

SVII.3 Details of important identified risks, important potential risks and missing information

There are no important identified risks, no important potential risks, and no missing information in the current RMP version.

SVII.3.1 Presentation of important identified risks

There are no important identified risks in the current RMP version.

SVII.3.2 Presentation of important potential risks

There are no important potential risks in the current RMP version.

SVII.3.3 Presentation of missing information

There is no missing information in the current RMP version.

PART II: Module SVIII – Summary of safety concerns

SVIII.1 Summary of the safety concerns

A summary of the safety concerns for naloxegol is presented in Table 12

Table 12: Summary of safety concerns

Important identified risks	None
Important potential risks	None
Missing information	None

PART III: PHARMACOVIGILANCE PLAN

III.1 Routine pharmacovigilance activities

The following routine pharmacovigilance (PV) activities beyond adverse reactions reporting and signal detection are performed for naloxegol.:

Specific adverse reaction follow-up questionnaire for gastrointestinal perforation

This form should provide 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

There are no other routine pharmacovigilance activities in the current RMP version.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are ongoing or planned at this point.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

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

PART V: RISK MINIMISATION MEASURES

V.1 Routine Risk minimisation measures

There are no safety concerns in this current RMP. Therefore, this section is not applicable.

V.2 Additional risk minimisation measures

Not applicable

V.3 Summary of risk minimisation measures

Not applicable

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.

VI.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

VI.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.

VI.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).

There are no important risks and missing information as in Table 13:

Table 13: **List of important risks and missing information**

Important identified risks	None
Important potential risks	None
Missing information	None

VI.2.2 Summary of important risks

There are no important identified risks, important potential risks or areas of missing information for Moventig.

VI.2.3 Post-authorisation development plan

VI.2.3.1 Studies which are conditions of the marketing authorisation

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

VI.2.3.2 Other studies in post-authorisation development plan

There are no other studies in post-authorisation development plan.

PART VII: ANNEXES

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's Name: Reporter's Specialty:
AE Number:	Reporter's Address: Phone Number:
Patient'sGender/Age/Height/Weight:	INDICATION for use of Naloxegol®? Naloxegol® Dosage?
Naloxegol®StartDate? Naloxegol®StopDate?	
Please carefully describe the exact nature of this event and how it was diagnosed:	
Carefully describe the time course and outcome of this event, especially with respect to the administration of Naloxegol®:	
Please briefly describe concomitant medication:	
Please provide all recent and past medical/surgical history:	
Can you share the high-level results of any recent diagnostic tests? Please briefly describe:	
Has this patient had a history of gastrointestinal obstruction or known peritoneal adhesions prior to Naloxegol® administration? If yes, please provide details.:	
Please provide any additional information that you feel is informative:	

Return completed form to Grünenthal GmbH

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

None