SWISS Summary of the Risk Management Plan (RMP) for Moventig® (naloxegol)

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The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary for Moventig (naloxegol) is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le medicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Moventig in Switzerland is the "Arzneimittelinformation / Information sur le medicament" (see www.swissmedic.ch) approved and authorized by Swissmedic.

Kyowa Kirin Saŕl is fully responsible for the accuracy and correctness of the content of the published summary RMP of Moventig.

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.

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.

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 the table below.

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	Safety in patients with cancer pain 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

Summary of important risks

Further information about the important risks and missing information for Moventig is provided in the table below.

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	**Study D3820R00009** Naloxegol Health Outcomes PASS
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	**Study D3820R00009** Naloxegol Health Outcomes PASS
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	Routine risk minimisation measures: SmPC Section 4.3, Contraindications SmPC Section 4.4, Special warnings and special precautions for use Routine risk minimisation activities recommending specific clinical measures to address the risk: 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	**Study D3820R00009** Naloxegol Health Outcomes PASS 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	**Study D3820R00009** Naloxegol Health Outcomes PASS **Study D3820R00006** Naloxegol Drug Utilization PASS
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 D3820R00009** Naloxegol Health Outcomes PASS **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	<u>Routine risk minimisation measures:</u> 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	**Study D3820R00009** Naloxegol Health Outcomes PASS
Missing Information - Safety in patients with cancer pain	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.3, Moventig should not be used in patients with cancer pain who are at heightened risk of GI perforation. SmPC Section 4.4, recommends caution when prescribing Moventig to patients with cancer-related pain PIL Section 2, Take special care
Additional pharmacovigilance activities	**Study D3820R00009** Naloxegol Health Outcomes PASS
Missing Information – Use in high risk CV patients	
Risk minimisation measures	Routine risk minimisation measures: None
Additional pharmacovigilance activities	**Study D3820R00009** Naloxegol Health Outcomes PASS **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 D3820R00009** Naloxegol Health Outcomes PASS **Study D3820R00008** Naloxegol US PMR CV Safety **Study D3820R00006** Naloxegol Drug Utilization PASS
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	**Study D3820R00009** Naloxegol Health Outcomes PASS **Study D3820R00006** Naloxegol Drug Utilization PASS
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	**Study D3820R00009** Naloxegol Health Outcomes PASS **Study D3820R00006** Naloxegol Drug Utilization PASS
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	**Study D3820R00009** Naloxegol Health Outcomes PASS **Study D3820R00006** Naloxegol Drug Utilization PASS
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	**Study D3820R00009** Naloxegol Health Outcomes PASS **Study D3820R00006** Naloxegol Drug Utilization PASS
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	**Study D3820R00009** Naloxegol Health Outcomes PASS **Study D3820R00006** Naloxegol Drug Utilization PASS

Post-authorisation development plan
Studies which are conditions of the marketing authorisation
There are no studies which conditions of the marketing authorisation or specific obligation of Moventig.

Other studies in post-authorisation development plan
Study short name and title:

D3820R00006: An Observational PASS of MOVENTIG (naloxegol) Drug Utilization in Selected European Populations

Purpose of the study:
The purpose of the study is to collect and assess data regarding the characteristics of patients prescribed naloxegol at time of first prescription, treatment patterns and identify predictors of length of naloxegol use.

Rationale and study objectives:

Non-interventional study with a design based on secondary use of data. This is a 3-year Drug Utilisation study (DUS) targeting a sample size of 3000 patients across national prescribing and patient registry database systems from 4 countries: Germany, UK, Norway and Sweden.

Patients in the targeted countries who are newly prescribed naloxegol will be identified for inclusion. Patients analysed in this study will be those who have at least 12 months of continuous data available prior to first prescription. The number of patients who do not have at least 12 months of prior data will be reported for completeness.

The main objectives of the study are to describe the characteristics of patients prescribed naloxegol at time of first prescription (demographics, targeted comorbidities, targeted co-medications, provider characteristics, and indication characteristics), and to describe treatment patterns, such as discontinuation of naloxegol (permanently during the observation period), switching from naloxegol to other drug(s), prescription of other drug(s) potentially used by patients with OIC in the same period when naloxegol is prescribed, re-starting naloxegol, continuous treatment with naloxegol during the study period, change in dosing.

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).

Study short name and title:

D3820R00009: Naloxegol Health Outcomes PASS

An Observational Post-Authorisation Safety Study (PASS) of MOVENTIG® (Naloxegol) Among Patients Aged 18 Years and Older Diagnosed with Non-Cancer Pain and Cancer Pain and Treated with Opioids Chronically in Selected European Populations

Purpose of the study:
The purpose of the study to monitor clinically important identified and potential risks within a cohort of patients treated with naloxegol to augment routine evaluation of the safety profile of naloxegol in clinical practice.

The exploratory purpose is to assess the incidence risk of CV-specific mortality, opioid withdrawal, abdominal pain, diarrhoea, syncope, and change in pain severity in patients treated with naloxegol, and by pre-specified sub-populations.

Rationale and study objectives:

In a retrospective new user's cohort design, all recipients of naloxegol will be followed in this study that have received the marketed drug in the course of ordinary clinical practice after authorization of the drug (the NIC). Patients in the targeted countries (currently the United Kingdom [UK], the Netherlands and Germany) who receive prescriptions for naloxegol will be identified for inclusion in the NIC, while patients in these countries who receive a prescription for a non-PAMORA laxative will be identified for inclusion in the CRC. All patients in this study will be ≥18 years of age; have ≥1 year of continuous data available; have exposure to current, regular opioid use; and have no prior exposure to PAMORA laxatives alvimopan, methylnaltrexone, or naloxone + opioid combination (including fixed-dose combinations). Patients will be grouped by cancer or non-cancer for analysis.

The main objectives of the study are to assess the incidence risk of bowel perforation, acute MI, stroke, all-cause mortality, and hypertension in patients treated with naloxegol (Naloxegol Inception Cohort [NIC]), patients treated with a non-peripherally acting mu-opioid receptor antagonist (PAMORA) laxative (concurrent reference cohort [CRC]), and by pre-specified sub populations that include patients aged ≥65 years, pregnant patients, patients with prior cardiovascular risk, patients with prior renal or hepatic impairment, patients with concurrent methadone use, and patients with concurrent use of cytochrome P450 (CYP) 3A inhibitors/ inducer or P-glycoprotein (P-gp) modulators.