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Summary of the risk management plan (RMP) for Moventig (naloxegol)

This is a summary of the risk management plan (RMP) for Moventig, which details the measures to be taken in order to ensure that Moventig is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Moventig, which can be found on Moventig's EPAR page.

Overview of disease epidemiology

Moventig is a medicine used to treat adults with constipation caused by use of pain relief medicines called opioids (such as codeine, hydrocodone, oxycodone, or morphine). It is given to patients who have not responded to treatment with standard laxatives.

Constipation is a condition where bowel movements are difficult to pass and occur less than 3 times per week, or where there is a feeling of incomplete emptying or blockage in the bowel. Opioid medicines are known to cause constipation. Some studies have reported that up to 90% of patients taking opioids develop opioid induced constipation (OIC), although estimates across studies vary widely. Laxative medicines can be used to relieve constipation, although many standard laxatives are not effective in constipation caused by opioids.

Summary of treatment benefits

The active substance in Moventig, naloxegol, works in the gut to block the effects of the opioids that cause constipation. Opioids work by attaching to specific receptors in the brain and spinal cord (called mu opioid receptors) to relieve pain. However, these receptors are also found in the gut and when opioids attach to the gut receptors, they reduce the movement of the gut and can cause constipation. Naloxegol attaches to mu opioid receptors in the gut and prevents opioids from causing constipation. By blocking receptors in the gut, Moventig reduces the constipation due to opioids, but it does not enter the brain in significant amounts it does not interfere with their pain relief effects.

Moventig has been shown to be effective at treating constipation in adults who had an inadequate response to laxatives in two main studies. The studies involved 1,352 adults with constipation caused by opioids that were being used to treat non-cancer pain, half of whom had an inadequate response to laxatives (720). People either received Moventig (at 12.5 and 25 mg) or placebo (a dummy treatment) for 12 weeks. The response to treatment was based on an improvement of the number of spontaneous bowel movements per week which had to be maintained for most of the duration of the study. When looking at the results of both main studies together, 48% (115 out of 241) of adults who previously had an inadequate response to laxatives and who took 25 mg Moventig responded to treatment compared with 30% (72 out of 239) of adults on placebo. For adults who took 12.5 mg Moventig and who previously had an inadequate response to laxatives, 43% (102 out of 240) responded to treatment..

Unknowns relating to treatment benefits

Most patients included in the clinical trials were white or black and experience in other ethnic groups is limited. A few patients were over 75 years old.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Side effects on the digestive system	Patients taking Moventig in clinical trials experienced side effects on the digestive system such as stomach cramps/pain, diarrhoea, flatulence (passing wind), nausea or vomiting. These effects are usually mild or moderate and gradually disappear with continued treatment. Approximately 1 in 20 patients stopped treatment with Moventig due to effects on the digestive system.	Patients should be advised to promptly report severe, persistent or worsening symptoms to their physician. Consideration may be given to lowering the dose to 12.5 mg in patients experiencing severe gastrointestinal adverse events depending upon the response and tolerability of individual patients
Withdrawal symptoms associated with opioids	Opioids work by binding to specific receptors in the brain to relieve pain. When a patient stops taking opioids after prolonged use or use at high doses, the patient may experience withdrawal symptoms, such as anxiety, chills, aches and pains, feeling or being sick, high blood pressure, and rapid heartbeat. Opioid receptors are also found in the gut and as Moventig acts on these receptors preventing opioids from attaching to them withdrawal symptoms may be seen. A small number of patients receiving Moventig in clinical trials showed signs of opioid withdrawal.	Patients should be informed of the risk of withdrawal symptoms. Patients should stop treatment in case of symptoms suggestive of withdrawal and consult their doctor.
Interactions with medicines interfering with the activity of certain enzymes (CYP3A4 and P-gp)	Use of Moventig with medicines that are cleared from the body in the same way as naloxegol may result in either an increase in naloxegol levels in the blood, with possible increase in side effects, or a decrease of naloxegol levels in the blood, with possible loss of effectiveness. Some herbal medicines may also affect naloxegol levels in the blood.	Patients should tell their doctor or let the pharmacist know if they are taking, have recently taken or might take any other medicines, including laxatives, herbal medicines and medicines obtained without a prescription. Patients should not drink large amounts of grapefruit juice while taking Moventig as it can increase blood levels of naloxegol. The medicines that may interact with naloxegol are listed in the prescribing

Risk	What is known	Preventability
		information and patient leaflet.

Important potential risks

Risk	What is known
Gastro-intestinal perforation (resulting in a hole in the wall of the gut)	A few patients treated with another medicine that works in a similar way to Moventig have developed a hole, or perforation in the gut wall. This may have been caused by other conditions that they had, such as ulcers, blockages, or cancer. No patients in clinical trials developed a hole in the gut wall, but patients with weakened gut walls may be at an increased risk of developing a hole, because of the way Moventig works on the digestive system.
Haemodynamic (blood flow) changes potentially leading to serious cardiovascular events (affecting the heart and blood vessels including effects on blood pressure and syncope)	In clinical studies (involving 2,134 patients), there were a total of 7 events of low blood pressure and fainting. Many of the patients who experienced these events had a medical history of a condition that could potentially cause low blood pressure or fainting and/or were on anti-hypertensive (high blood pressure) medications which are known to carry a risk of these events. In clinical studies, approximately 4 patients in every 100 patients treated with Moventig at a dose of 25 mg once per day had increases in blood pressure. A lower proportion of patients (approximately 1 to 2 patients in every 100 patients) had increases in blood pressure when treated with Moventig 12.5 mg once a day. Of more than 1,000 patients in clinical trials, 5 patients had increases in blood pressure, which were medically serious.
Off-label use	Off-label use is use of a medication in a way that is not described in the approved prescribing information. There is a potential for Moventig to be used off-label to treat patients who are younger than 18 years old, patients with constipation not caused by opioids and in patients who have an adequate response to laxatives. There is also a potential for off-label use of Moventig at a dose of 12.5 mg once a day, which is only recommended for certain types of patients i.e. patients who cannot use the 25 mg dose of Moventig.
Interference with opioid-mediated analgesia (pain relief)	Moventig may act on the opioid receptors in the brain and interfere with the pain relieving effects of opioids in patients whose 'blood - brain barrier' that separates the bloodstream from the brain is altered. In 2 clinical studies where patients were treated for 3 months, more patients who received Moventig reported back pain or pain in the extremities (e.g. pain in the arms or legs) compared with patients who were given placebo (a dummy treatment). In the 3-month studies, less than 5 patients in every 100 patients had back pain (compared with 2 in every 100 patients in the placebo group), and around 2 patients in every 100 patients had pain in the extremities (compared with less than 1 patient in every 100 in the placebo group). However, in a long-term safety study, where Moventig was given for up to 1 year, the proportion of patients who had back pain and/or pain in the extremities was similar in Moventig-treated patients and those who were given standard of care.

Missing information

Risk	What is known
Patients using methadone	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 program, 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.
Patients with cancer-related pain	There is limited experience with the use of Moventig to treat constipation in patients given opioids for cancer-related pain. Therefore caution should be used when prescribing Moventig to such patients.
Patients at high risk of cardiovascular events	In the clinical trial programme, Moventig was not studied in patients who had a heart attack within the last 6 months and other problems with their heart. Moventig should be used with caution in these patients. A study performed with Moventig in healthy volunteers did not indicate that Moventig prolongs the heart rhythm (causing a phenomenon called prolongation of the QT interval). A retrospective assessment of cardiovascular risk showed that two thirds of patients included in phase 3 studies had at least one cardiovascular risk factor and one third of the patients had heart disease, diabetes, or 2 or more cardiovascular risk factors. There were no differences in safety or efficacy noted in these groups of patients.
Long-term (more than 1 year) safety and effectiveness	In the clinical studies, Moventig treatment lasted for a maximum of 1 year, and was shown to be generally safe and well tolerated. No data are available beyond one year.
Patients aged 75 years and older	Limited data are available in patients who are 75 years and older. However, patients over 65 years of age were included in clinical studies and no dose adjustment is needed for these patients.
Patients with reduced kidney function	As the kidneys do not play a major part in the removal of the active substance in Moventig, naloxegol, from the body, reduced kidney function is only expected to have a small effect on the blood levels of naloxegol. In a clinical study in patients with kidney disorders, including patients with moderately and severely reduced kidney function, 2 out of 8 patients in either groups, had an amount of naloxegol in the blood over time that was up to 10 times higher than patients with normal kidney function. It is possible that other problems in these patients were responsible for the increased blood levels. The blood levels of naloxegol in patients with end-stage kidney failure on dialysis were unchanged and patients had the same blood levels of naloxegol as patients with normal kidney function.

Risk	What is known
	The starting dose for patients with moderate or severely-reduced kidney function is 12.5 mg. The dose can be increased to 25 mg if tolerated well. Treatment with Moventig should be stopped in any patient with reduced kidney function who develops significant side effects.
Patients with reduced liver function	No dose adjustment is required for patients with mild to moderate liver impairment. Safety and efficacy have not been established in patients with severe liver impairment. Use of Moventig in patients with severe liver impairment is not recommended.
Patients from different ethnic groups	Most of the patients included in clinical studies were white or black. The effect of race on the pharmacokinetics of naloxegol is small (approximately 20 % decrease in the total amount of naloxegol on the blood over time) and, therefore, no dose adjustment is necessary.
Use in children	Studies investigating the use of Moventig in children have not been performed.
Use in pregnant or breastfeeding women	If a patient is pregnant, or are planning to have a baby, they should speak to their doctor, pharmacist or nurse for advice before taking Moventig. The use of Moventig during pregnancy is not recommended. The use of Moventig during breastfeeding is not recommended.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as ‘routine risk minimisation measures’.

The SmPC and the package leaflet are part of the medicine’s product information. The product information for Moventig can be found on Moventig’s EPAR page.

This medicine has no additional risk minimisation measures.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study / activity (including study number)	**Objectives**	**Safety concerns / efficacy issue addressed**	**Status**	**Planned date for submission of (interim and) final results**
Study D3820C00016 A study of naloxegol in children aged 6 months to 18 years	To investigate blood levels and safety of naloxegol in children aged 6 months to 18 years.	Effects in children	Planned for 3Q2014	Final report estimated to be available by 2Q2017.

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Naloxegol post-market observational drug utilisation study (D2288R00081) Pending approval	To describe demographic, clinical, and treatment characteristics in the baseline of patients treated with naloxegol. To describe treatment pattern characteristics of naloxegol utilisation at initiation and follow-up.	Important identified and potential risks. Missing information.	Submission of protocol by January 2015	First annual report to be delivered end of 4Q 2016 and every year thereafter until completion. These dates are still to be confirmed.
Naloxegol post-market observational safety study in patients taking opioids for cancer pain (D2288R00082) Pending approval	To estimate event rates for pre-specified health outcomes of interest among naloxegol-treated patients with active cancer pain.	Important identified and potential risks Missing information	Submission of protocol by January 2015	First annual report to be delivered by the end of 4Q2016 and every year thereafter completion. Approved protocol by early 1Q2015
Naloxegol post-market observational safety study in patients taking opioids for non-cancer pain (D2288R00084) Pending approval	To estimate event rates for pre-specified health outcomes of interest among naloxegol-treated patients with non-cancer pain and a concurrent comparator of regular opioid users with non-cancer pain. To estimate event	Important identified and potential risks Missing information	Submission of protocol by January 2015	First annual report delivered to be by the end of 4Q2016 and every year thereafter until completion

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	rates for pre-specified health outcomes of interest among pre-specified sub-populations of both naloxegol-treated patients and a concurrent comparator of regular opioid users with non-cancer pain.			
Proposed and pending approval A US post-marketing, comparative, observational study to evaluate the cardiovascular safety of naloxegol in patients with non-cancer pain in comparison to other treatments for opioid induced constipation	This observational study will characterize the cardiovascular risk and Major Adverse heart events, such as myocardial infarction, Cardiovascular attack, and cardiac death.	Cardiovascular risk.	Final Protocol Submission: May 2015. Study Completion: December 2021	Final report: December 2023 Annual reports: Starting in 2016 until study completion

Studies which are a condition of the marketing authorisation

None of the above studies are a condition of the marketing authorisation.

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 12-2014.