Summary of risk management plan for Rizmoic (naldemedine)

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

Rizmoic's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Rizmoic should be used.

This summary of the RMP for Rizmoic should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

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

I. The medicine and what it is used for

Rizmoic is authorised for the treatment of opioid-induced constipation (OIC) in adults who have previously been treated with a laxative (see SmPC for the full indication). It contains naldemedine as the active substance and it is given orally.

Further information about the evaluation of Rizmoic's benefits can be found in Rizmoic'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/rizmoic

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

Important risks of Rizmoic, together with measures to minimise such risks and the proposed studies for learning more about Rizmoic'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 (eg, 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, including PSUR assessment 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 Rizmoic is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Rizmoic 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 Rizmoic. 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 (eg, on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Abdominal pain, diarrhoea and vomiting Opioid withdrawal syndrome
Important potential risks	Gastrointestinal perforation Anti-analgesic effect due to centrally-mediated opioid receptor antagonism
Missing information	Long-term use (more than 1 year) safety Patients with severe hepatic impairment Use in children Use in pregnant or breast-feeding women Patients at high risk of cardiovascular events Patients aged 75 years and older Patients with severe renal impairment Effect of concurrent methadone use

II.B Summary of important risks

Important identified risk: Abdominal pain, diarrhoea and vomiting	
Evidence for linking the risk to the medicine	Naldemedine clinical studies and published literature. The safety of naldemedine 0.2 mg was evaluated in patients with chronic non-cancer pain and OIC (N=1163; Global Phase 3 up to first 12 weeks) and in patients with cancer and OIC (N=155; Japan cancer studies with control arm). Data from the clinical studies can provide an accurate estimate of the frequency of abdominal pain, diarrhoea, and vomiting that are expected to occur in clinical practice.
Risk factors and risk groups	Gastrointestinal complications (constipation, impaction, bowel obstruction, diarrhoea and radiation enteritis) are common problems for cancer patients as the growth and spread of cancer contributes to these conditions (NIH National Cancer Institute, 2016). In the clinical studies patients with cancer and OIC treated with naldemedine (24.5%; 38/155) were found to be at greater risk of diarrhoea than patients with chronic non-cancer pain and OIC treated with naldemedine (5.6%; 65/1163). Similarly, placebo-treated patients with cancer and OIC were found to be at a greater risk of diarrhoea (11.8%; 18/155) than placebo-treated patients with chronic non-cancer pain and OIC (1.5%; 17/1163). Other risk factors for abdominal pain, diarrhoea and vomiting include certain medications. Medications that are recognised to cause diarrhoea in at least 20% of patients include α-glucosidase inhibitors, prostaglandins, tyrosine kinase inhibitors, highly active antiretroviral therapy, biguanides, colchichine, diacerein and

	auronofin (gold salt), whereas antibiotics, chemotherapeutic agents, cholinergic drugs, digoxin, immunosuppresants, metoclopramide, orlistat, osmotic laxatives, selective serotonin reuptake inhibitors (SSRIs), ticlopidine and poorly or non-absorbable carbohydrates are recognised to cause diarrhoea in at least 10% of patients (Abraham, 2010). NSAIDs are another common cause of gastrointestinal symptoms (Fosslien, 1998) and both non-selective non-aspirin NSAIDs (28%), and COX-2 NSAIDs (12%) are frequently used in regular opioid users for the treatment of pain (Parsells Kelly, 2008). A number of conditions may also cause abdominal pain, diarrhoea and vomiting. Abdominal pain may be caused by inflammatory conditions of the upper abdomen, functional problems of the abdomen, cancers of the upper abdomen, vascular problems, bowel obstruction, urinary tract problems, abdominal or chest wall pain, non-abdominal causes or pelvic problems in women (Schiller, 2013). Most cases of acute, watery diarrhoea are caused by viruses (viral gastroenteritis) including rotavirus in children and norovirus in adults whereas chronic bloody diarrhoea may be due to inflammatory bowel disease including ulcerative colitis or Crohn's disease (Ochoa, 2012). Other less common causes include ischaemia of the gut, infections, radiation therapy and colon cancer or polyps. The two major causes of fatty or malabsorptive diarrhoea are impaired digestion of fats due to low pancreatic enzyme levels and impaired absorption of fats due to small bowel disease (Ochoa, 2012). There are multiple causes of vomiting including chemotherapy medicines, infections of the gastrointestinal tract, infections outside the gastrointestinal tract, bacterial toxins in food, pregnancy, motion sickness, alcohol intoxication, inflammation of the abdominal organs such as pancreatitis, Crohn's disease or ulcerative colitis, intestinal blockage, gastroparesis, ileus or pseudoobstruction, migraine headaches, brain tumours, seizures, head trauma, multiple sclerosis, hormonal disorders, renal failure, radiation therapy, psychiatric disorders, cyclic vomiting syndrome, physical or emotional pain and myocardial infarction (Porter, 2010).
Risk minimisation measures	Routine risk minimisation measures: • *Listed as adverse reactions in SmPC section 4.8* • *Listed as side effects in PL section 4* • *Warning in SmPC section 4.4 for the patient to report severe reactions to their physician for monitoring and treatment as needed* • *Warning in PL section 2 for the patient to report severe diarrhoea or stomach ache to their doctor for monitoring and treatment if needed* • *Guidance in SmPC section 4.9 that dose-dependent gastrointestinal reactions have occurred in overdose and to provide appropriate supportive care* • *Legal status (prescription only medicine)* Additional risk minimisation measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *Retrospective database cohort study* See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk: Opioid withdrawal syndrome	
Evidence for linking the risk to the medicine	Naldemedine clinical studies and published literature. The safety of naldemedine 0.2 mg was evaluated in patients with chronic non-cancer pain and OIC (N=1163; Global Phase 3 up to first 12 weeks) and in patients with cancer and OIC (N=155; Japan cancer studies with control arm). Data from the clinical studies can provide an accurate estimate of the frequency of opioid withdrawal syndrome that is expected to occur in clinical practice.
Risk factors and risk groups	Patients with disruptions to the BBB, including primary brain malignancies, CNS metastases or other inflammatory conditions, active multiple sclerosis and advanced Alzheimer's disease, are at increased risk of opioid withdrawal syndrome. Maternal exposure to naldemedine during pregnancy may precipitate opioid withdrawal in a foetus due to the immature foetal BBB, and as such foetuses exposed *in utero* are at increased risk.
Risk minimisation measures	Routine risk minimisation measures: • *Listed as an adverse reaction in SmPC section 4.8* • *Listed as a side effect in PL section 4* • *Warning in SmPC section 4.4 for the patient to discontinue naldemedine and to contact their physician if opioid withdrawal occurs* • *Warning in PL section 2 for the patient to contact their doctor and stop taking naldemedine should they develop opioid withdrawal symptoms* • *Warning in PL section 4 for the patient to stop taking naldemedine and to contact their doctor if they get a combination of 3 or more symptoms of opioid withdrawal syndrome on the same day* • *Warning in SmPC section 4.4 to consider the overall benefit-risk of naldemedine in patients with disruptions to the blood-brain barrier and to closely monitor symptoms* • *Warning in PL section 2 for the patient to talk to their doctor before taking naldemedine if they have cancer of the brain or central nervous system, multiple sclerosis, or Alzheimer's disease and to contact their doctor immediately if they develop opioid withdrawal symptoms* • *Guidance in SmPC section 4.6 about the risk of opioid withdrawal in the foetus following exposure in utero and a recommendation for use during pregnancy* • *Guidance in SmPC section 4.6 about the risk of opioid withdrawal in the breast-fed infant and guidance for use during breast-feeding* • *Guidance in PL section 2 for the patient to ask for advice if they are pregnant or breast-feeding, think they may be pregnant or are planning to have a baby before taking naldemedine* • *Guidance in SmPC section 4.9 to provide appropriate supportive care in the case of overdose and to monitor for opioid withdrawal syndrome* • *Guidance in PL section 3 for the patient to contact their doctor or go to hospital if they have taken more naldemedine than they should* • *Legal status (prescription only medicine)* Additional risk minimisation measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *Retrospective database cohort study* See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Gastrointestinal perforation	
Evidence for linking the risk to the medicine	Naldemedine clinical studies and published literature. The safety of naldemedine 0.2 mg was evaluated in patients with chronic non-cancer pain and OIC (N=1163; Global Phase 3 up to first 12 weeks) and in patients with cancer and OIC (N=155; Japan cancer studies with control arm). Data from the clinical studies can provide an accurate estimate of the frequency of gastrointestinal perforation that may occur in clinical practice.
Risk factors and risk groups	Cases of gastrointestinal perforation have been reported with use of peripherally-acting opioid antagonists (Relistor SmPC) in patients with conditions that may be associated with localised or diffuse reduction of structural integrity of the wall of the gastrointestinal tract (eg, peptic ulcer disease, Ogilvie's syndrome, diverticular disease and underlying malignancies of the gastrointestinal tract or peritoneal metastases). Patients with other conditions which might result in impaired integrity of the gastrointestinal tract wall (eg, Crohn's disease) are also at increased risk. Strong laxatives have been associated with gastrointestinal perforation. A perforated diverticulum was reported in a 73-year-old man treated with Picolax (sodium picosulphate) considered due to diverticular disease but precipitated by the Picolax in the presence of a distal obstructing carcinoma (Phipps, 1987). In another case a large bowel infarction (as opposed to perforation) causing peritonitis was reported after the administration of Picolax in a 75-year-old female patient (Bowyer, 1987). Administration of a strong laxative to a patient who has an obstruction in the intestinal tract or a patient suspected of having such a condition may be at increased risk of experiencing the symptoms leading to gastrointestinal perforation.
Risk minimisation measures	Routine risk minimisation measures: • *Contraindication in SmPC section 4.3 for patients with or at risk of gastrointestinal perforation* • *Warning in PL section 2 for the patient not to take naldemedine if their bowel is blocked or perforated, or there is a high risk of their bowel becoming blocked as this may cause a hole in their bowel wall* • *Warning in SmPC section 4.4 for the overall risk-benefit of naldemedine to be considered in patients with impaired integrity of the gastrointestinal tract wall, that patients should be monitored and to discontinue naldemedine if gastrointestinal perforation is suspected* • *Warning in PL section 2 for the patient to talk to their doctor or pharmacist before taking naldemedine if they suffer from a disease which may affect their bowel wall* • *Warning in PL section 2 for the patient to talk to their doctor immediately and to stop taking naldemedine if they develop severe, lasting or worsening stomach pain as this could be a symptom of developing a hole in their bowel wall* • *Legal status (prescription only medicine)* Additional risk minimisation measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *Retrospective database cohort study* See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Anti-analgesic effect due to centrally-mediated opioid receptor antagonism	
Evidence for linking the risk to the medicine	Naldemedine clinical studies and published literature. The safety of naldemedine 0.2 mg was evaluated in patients with chronic non-cancer pain and OIC (N=1163; Global Phase 3 up to first 12 weeks) and in patients with cancer and OIC (N=155; Japan cancer studies with control arm). Data from the clinical studies can provide an accurate estimate of the frequency of anti-analgesic effect due to centrally-mediated opioid receptor antagonism that may occur in clinical practice.
Risk factors and risk groups	Patients with disruptions to the BBB, including primary brain malignancies, CNS metastases or other inflammatory conditions, active multiple sclerosis and advanced Alzheimer's disease, are at increased risk of anti-analgesic effect due to centrally-mediated opioid receptor antagonism.
Risk minimisation measures	Routine risk minimisation measures: • *Warning in SmPC section 4.4 for the overall benefit-risk of naldemedine to be considered in patients with disruptions to the blood-brain barrier because of possible reduced analgesia* • *Warning in PL section 2 for the patient to talk to their doctor before taking naldemedine if they have cancer of the brain or central nervous system, multiple sclerosis, or Alzheimer's disease and to contact their doctor immediately if the opioid medicine no longer controls their pain* • *Legal status (prescription only medicine)* Additional risk minimisation measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *Retrospective database cohort study* See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Long-term use (more than 1 year) safety	
Risk minimisation measures	Routine risk minimisation measures: • *Legal status (prescription only medicine)* Additional risk minimisation measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *Retrospective database cohort study* See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Patients with severe hepatic impairment	
Risk minimisation measures	Routine risk minimisation measures: • *Guidance in SmPC section 4.2 that use of naldemedine in patients with severe hepatic impairment is not recommended* • *Guidance in PL section 2 that the patient should talk to their doctor or pharmacist before taking naldemedine if they have severe liver disease such as alcoholic liver disease, viral liver infection or impaired liver function* • *Warning in SmPC section 4.4 that naldemedine has not been studied in patients with severe hepatic impairment and that use in these patients is not recommended* • *Information in SmPC section 5.2 that the effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of naldemedine was not evaluated* • *Legal status (prescription only medicine)* Additional risk minimisation measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *Retrospective database cohort study* See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Use in children	
Risk minimisation measures	Routine risk minimisation measures: • *Guidance in SmPC section 4.1 on the indicated population which specifies use in adults* • *Guidance in PL section 1 on the intended use of naldemedine in adult patients* • *Guidance in SmPC section 4.2 that the safety and efficacy of naldemedine in children and adolescents have not been established and that no data are available* • *Guidance in PL section 2 that naldemedine is not for children or adolescents because the effects in children and adolescents are not known* • *Information in SmPC section 5.2 that the pharmacokinetics of naldemedine in the paediatric population has not been studied* • *Legal status (prescription only medicine)* Additional risk minimisation measures: • *None*

Missing information: Use in pregnant or breast-feeding women	
Risk minimisation measures	Routine risk minimisation measures: • *Guidance in SmPC section 4.6 about the risk of opioid withdrawal in the foetus following exposure in utero and a recommendation for use during pregnancy* • *Guidance in SmPC section 4.6 about the risk of opioid withdrawal in the breast-fed infant and guidance for use during breast-feeding* • *Guidance in PL section 2 for the patient to ask for advice if they are pregnant or breast-feeding, think they may be pregnant or are planning to have a baby before taking naldemedine* • *Information in SmPC section 5.3 relating to in vivo findings concerning embryo-fetal development* • *Legal status (prescription only medicine)*

Missing information: Use in pregnant or breast-feeding women	
	Additional risk minimisation measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *Retrospective database cohort study* See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Patients at high risk of cardiovascular events	
Risk minimisation measures	Routine risk minimisation measures: • *Warning in SmPC section 4.4 that patients with a recent history of myocardial infarction, stroke or transient ischaemic attack were not studied and these patients should be clinically monitored when taking naldemedine* • *Guidance in PL section 2 for the patient to talk to their doctor or pharmacist before taking naldemedine if they have had a heart attack within the last 3 months or if they have other severe heart problems* • *Legal status (prescription only medicine)* Additional risk minimisation measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *Retrospective database cohort study* See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Patients aged 75 years and older	
Risk minimisation measures	Routine risk minimisation measures: • *Guidance in SmPC section 4.2 that naldemedine should be initiated with caution in patients 75 years old and older due to limited therapeutic experience* • *Legal status (prescription only medicine)* Additional risk minimisation measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *Retrospective database cohort study* See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Patients with severe renal impairment	
Risk minimisation measures	Routine risk minimisation measures: • *Guidance in SmPC section 4.2 that use of naldemedine in patients with severe renal impairment is limited and therefore patients should be clinically monitored when initiating naldemedine* • *Information in SmPC section 5.2 that the pharmacokinetics of naldemedine is similar in patients with mild, moderate or severe renal impairment, patients with ESRD requiring haemodialysis and healthy subjects* • *Legal status (prescription only medicine)* Additional risk minimisation measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *Retrospective database cohort study* See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Effect of concurrent methadone use	
Risk minimisation measures	Routine risk minimisation measures: • *Legal status (prescription only medicine)* Additional risk minimisation measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *Retrospective database cohort study* See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

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

II.C.2 Other studies in post-authorisation development plan

Retrospective database cohort study

Purpose of the study: The primary objective of this post-authorisation safety study is to assess the incidence risk of major cardiovascular (CV) outcomes (ie, acute myocardial infarction, stroke, CV death) and gastrointestinal (GI) perforation, and to characterise the safety profile of naldemedine in routine clinical practice for the treatment of OIC in patients with chronic opioid use for non-cancer and cancer pain, both overall and for population subgroups under-represented in the clinical development programme

References for the Summary of the risk management plan

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