PART VI: SUMMARY OF ACTIVITIES IN THE RISK MANAGEMENT PLAN BY PRODUCT

VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary table of Safety concerns

Important identified risks (s)	• Respiratory and circulatory impairment (due to high dose opioid intake concomitant with naltrexone treatment) • Withdrawal syndrome • Impaired and/or altered hepatic function • Impaired renal function • Suicide
Important potential risks	Nil
Missing information	• Use in children and adolescents under 18 years of age • Use in elderly • Use during pregnancy • Use in lactating women

VI.1.2 Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan (if applicable)

Not applicable.

VI.1.3 Summary of Post authorisation efficacy development plan (if applicable)

Not applicable.

VI.1.4 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks: Respiratory and circulatory impairment (due to high dose opioid intake concomitant with naltrexone treatment)	Section 4.4: High dose opioid intake, concomitant with Naltrexone treatment, can lead to life-threatening opioid poisoning from respiratory and circulatory impairment. If the patient needs opioid treatment, e.g. opioid analgesia or anesthesia in emergency situations, the dose needed may be higher than normal. In these cases, the respiratory depression and circulatory effects will be more profound and longer lasting. Symptoms related to release of histamine (diaphoresis, itching and other skin and mucocutaneous manifestations) can also be manifested more easily. The patient requires specific attention and care in these situations. During treatment with naltrexone, painful conditions should be treated with non-opioid analgesia only.	Currently available data does not support the need for additional risk minimization activities.

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
	Patients should be warned that large doses of opioids to overcome the blockade may after the cessation of the naltrexone result in an acute opioid overdose, with possible fatal outcome. Patients might be more sensitive to opioid containing medicines after treatment with naltrexone.	
Important identified risks: Withdrawal syndrome	Section 4.2: Naltrexone administered to opioid-dependent persons can cause life-threatening withdrawal symptoms. Patients suspected of using or being addicted to opioids must undergo a naloxone provocation test, unless it can be verified that the patient has not taken any opioids for 7-10 days (urine test) prior to the initiation of treatment with naltrexone. Section 4.3: Contraindicated to Opioid addicted patients with a current abuse of opioids since an acute withdrawal syndrome may ensue. Section 4.4: Should naltrexone be used in opioid-dependent patients a withdrawal syndrome may occur rapidly: the first symptoms can	Currently available data does not support the need for additional risk minimization activities.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	occur within 5 minutes, the last after 48 hours. The treatment of withdrawal symptoms is symptomatic. Patients suspected of using or being addicted to opioids must undergo a naloxone provocation test, unless it can be verified that the patient has not taken any opioids for 7-10 days (urine test) prior to the initiation of treatment with naltrexone. A withdrawal syndrome precipitated by naloxone will be of shorter duration than withdrawal precipitated by naltrexone. The recommended procedure is as follows: Intravenous provocation □ Intravenous injection of 0.2 mg naloxone □ If after 30 seconds no adverse reactions occur, a further i.v. injection of 0.6 mg naloxone may be administered. □ The patient should be observed continuously for 30 minutes for any detectable sign of withdrawal symptoms. If any symptoms of withdrawal occur naltrexone-therapy must not be undertaken. If the test-result is negative the treatment can be initiated. If any doubt exists that the patient is opioid-free, the challenge may be repeated	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	with the dosage of 1.6 mg. If no reaction occurs after this, 25 mg of naltrexone hydrochloride can be administered to the patient. A naloxone hydrochloride provocation test should not be made in patients with clinically prominent withdrawal symptoms nor in any case of a positive urine test for opioids.	
Important identified risks: Impaired and/or altered hepatic function	Section 4.3: Contraindicated to patients with Severe hepatic impairment Section 4.4: It is not uncommon for alcohol abusing individuals to show signs of impaired hepatic function. Abnormal hepatic function test parameters have been reported in obese and elderly patients receiving naltrexone in dosages higher than recommended (up to 300 mg/day). Hepatic function controls should be made before and during treatment. Special attention should be paid to patients with hepatic enzyme levels in serum exceeding three times the normal value and patients with renal impairment.	Currently available data does not support the need for additional risk minimization activities.

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
	Naltrexone is extensively metabolised by the liver and excreted predominantly in the urine. Therefore, caution should be observed in administering the medicinal product to patients with impaired hepatic or renal function. Liver function tests should be carried out both before and during treatment. Section 4.8: Rare (≥1/10,000 to <1/1,000): Gastrointestinal disorder: Hepatic disorder Section 5.3: There is some evidence on hepatotoxicity with increasing dose, since reversible increases of liver enzymes has been found in humans with therapeutic and higher doses.	
Important identified risks: Impaired renal function	Section 4.3: Contraindicated to patients with Severe renal impairment Section 4.4: Special attention should be paid to patients with hepatic enzyme levels in serum exceeding three times the normal value and	Currently available data does not support the need for additional risk minimization activities.

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
	patients with renal impairment. Naltrexone is extensively metabolised by the liver and excreted predominantly in the urine. Therefore, caution should be observed in administering the medicinal product to patients with impaired hepatic or renal function. Liver function tests should be carried out both before and during treatment. Section 4.8: Common (≥1/100 to <1/10): Renal and urinary disorder: urine retention	
Important identified risks: Suicide	Section 4.8: Rare (≥1/10,000 to <1/1,000): Psychiatric disorders: suicidal ideation, attempted suicide	Currently available data does not support the need for additional risk minimization activities.
Missing information: Use in children and adolescents under 18 years of age	Section 4.2: Naltrexone should not be used in children and adolescents under 18 years of age, since clinical data in this age-group are lacking. Safe use in children has not been established.	Currently available data does not support the need for additional risk minimization activities.

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Missing information: Use in elderly	Section 4.2: There are insufficient data on the safety and efficacy of naltrexone for the indication of alcohol dependence and opiod dependence in elderly patients.	Currently available data does not support the need for additional risk minimization activities.
Missing information: Use during pregnancy	Section 4.6: There are no clinical data on naltrexone hydrochloride use in pregnancy. The data are insufficient to establish clinical relevance. The potential risk for humans is unknown. Naltrexone should only be given to pregnant women when, in the judgement of the attending physician the potential benefits outweigh and the possible risk. Section 5.3: Naltrexone (100 mg/kg, approximately 140 times the human therapeutic dose) caused a significant increase in pseudo-pregnancy in the rat. A decrease in the pregnancy rate of mated female rats also occurred. The relevance of these observations to human fertility is not known. Naltrexone has been shown to have an	Currently available data does not support the need for additional risk minimization activities.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	embryocidal effect in the rat and rabbit when given in doses approximately 140 times the human therapeutic dose. This effect was demonstrated in rats dosed with 100 mg/kg of naltrexone prior to and throughout gestation, and rabbits treated with 60 mg/kg of naltrexone during the period of organogenesis.	
Missing information: Use in lactating women	Section 4.6: There are no clinical data on naltrexone HCl use in lactation. It is unknown whether naltrexone or 6-beta-naltrexol is excreted in human breast milk. During treatment breast feeding is not recommended.	Currently available data does not support the need for additional risk minimization activities.

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Alcohol dependence:

In the United Kingdom (UK), 51% of English pupils (age 11 to 15) in 2008 reported ever having an alcoholic drink, an increase from 2003 when the figure was 39%. About 48-49% of drinking occasions lead to intoxication in the UK among 15-16 year olds (1995-1999).

The Alcohol Needs Assessment Research Project (ANARP) in England found the prevalence of alcohol dependence to be 4% in 16- to 64-year-old adults: 6% of men and 2% of women. This equates to a population of 1.1 million people in England with alcohol dependence in 2000. This population increased to 1.6 million in 2007. In terms of productivity, alcohol contributes to absenteeism, accidents in the workplace and decline in work performance. Up to 17 million working days are lost annually in the UK due to alcohol-related absences and 58,000 working years are lost annually due to premature deaths related to alcohol.

Opioid dependence:

Since 2009, the estimated overall global prevalence of current opioid use was between 0.3% and 0.5%, which equals to 21 to 35 million people, including nearly 18 million people in the United States. Substantial regional differences in abuse patterns exist. In the majority of Europe, Africa, and Asia, heroin is the most commonly illegally consumed opioid. In the Americas and Oceania (Australia and New Zealand), illegally diverted or misused prescription opioids (e.g., codeine, hydrocodone, morphine, hydromorphone, oxycodone, meperidine) are the primary opioids of abuse. However, some African and Asian nations have reported a surge in prescription opioid abuse in the last decade. Traditional opium-cultivating countries and their neighbors contain the majority of raw opium users. Although comprising less than 5% of the world population, Americans consume roughly 80% of the worldwide opioid supply .

VI.2.2 Summary of treatment benefits

Opioid-dependence:

In a, 24-week trial, 250 patients with opiate dependence were given monthly injections of an extended-release formulation of 380 mg of naltrexone or placebo. The study found substantial benefit in the actively treated group, with abstinence rates of 90% compared with 35%.

Alcohol dependence:

Through year 2001 there were 14 Randomised Clinical Trials assessing the effectiveness of naltrexone compared with placebo for treating alcoholism, enrolling 2127 subjects, in five

countries. There is strong evidence that naltrexone significantly reduces alcohol relapses to heavy drinking, the frequency and the quantity of alcohol consumption in those who drink, and alcohol craving

No efficacy studies have been conducted for Naltrexone Accord considering its similarity to the innovator product.

VI.2.3 Unknowns relating to treatment benefits

The efficacy and safety of naltrexone has not been established in the following population:

- Use in children and adolescents under 18 years of age
- Use in elderly
- Use during pregnancy
- Use in lactating women

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Respiratory and circulatory impairment (due to high dose opioid intake concomitant with naltrexone treatment)	Talk to your doctor or pharmacist before taking Naltrexone if patient needs opioid treatment e.g. opioid analgesic or anaesthesia in emergency situation, opioid dose is higher to achieve the therapeutic effect. In these cases respiratory depression and circulatory effect will be more profound and longer	Yes During treatment with naltrexone, painful conditions should be treated with non-opioid pain relieving medicines only.

Risk	What is known	Preventability
	lasting	
Withdrawal syndrome (discontinuation syndrome)	Naltrexone administered to opioid-dependent persons can cause life-threatening withdrawal symptoms. Naltrexone treatment must begin only when the opioid has been discontinued for a sufficiently long period (about 5 to 7 days for heroin and at least 10 days for methadone).	Yes Do not take Naltrexone if patients have withdrawal symptoms after naloxone hydrochloride administration
Impaired and/or altered hepatic function (impair/compromise the liver and its function)	Liver function test abnormalities have been reported in obese and elderly patients taking naltrexone who have no history of drug abuse. Like all medicines, this medicine can cause side effects and can affect your liver function. Liver disorder (including inflammation of liver)	Yes Patients must not take naltrexone if they have an acute liver infection or if their liver function is poor Liver function tests should be carried out both before and during treatment.
Impaired renal function (kidney dysfunction, kidney insufficiency, kidney impairment (disorder))	Naltrexone is extensively metabolised by the liver and excreted predominantly in the urine. Therefore, caution should be observed in administering the	Yes Patients are advised to talk to their doctor or pharmacist before taking Naltrexone if they have

Risk	What is known	Preventability
	medicinal product to patients with impaired liver or kidney function. Common side effects: Urine retention Uncommon side effects: Increased urination Inflammation of urinary bladder	liver or kidney diseases.
Suicide	This medicine can rarely cause side effects such as Suicidal thoughts, Attempt to suicide	Yes Patients are advised to talk to doctor or pharmacist if they get any such side effects

Important Potential Risk:

Risk	What is known
Nil	

Missing information

Risk	What is known
Use in children and adolescents under 18 years	Naltrexone should not be used in children and adolescents under 18 years of age, since clinical data in this age-group are

of age	lacking. Safe use in children has not been established.
Use in elderly	There are insufficient data on the safety and efficacy of naltrexone for this indication in elderly patients.
Use during pregnancy	The safety of Naltrexone during pregnancy has not been demonstrated. If you are pregnant or think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
Use in lactating women	It is not known whether naltrexone is excreted in breast milk. Because the safety of using naltrexone in neonates and children has not been demonstrated, breast-feeding is not advised while using naltrexone.

VI.2.5 Summary of additional risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimization measures.

VI.2.6 Planned post authorisation development plan (if applicable)

No studies planned.

VI.2.7 Summary of changes to the risk management plan over time

Version	Date	Safety concerns	Comment
2.0	09 May 2014	Following safety concerns are added as per Preliminary Variation Assessment Report (NL/H/1151/001/II/003): **Important identified risks:** Respiratory and circulatory impairment (due to high dose opioid intake concomitant with naltrexone treatment) Withdrawal syndrome Impaired and/or altered hepatic function Impaired renal function Suicide **Missing information:** Use in children and adolescents under 18 years of age Use in elderly Use during pregnancy Use in lactating women	Part VI.2.1 Overview of disease epidemiology and VI.2.2 Summary of treatment benefits have been updated.