Part VI: Summary of the Risk Management Plan

Summary of risk management plan for SUBUTEX prolonged-release solution for injection (buprenorphine)

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

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

Important new concerns or changes to the current ones will be included in updates of SUBUTEX prolonged-release injection's RMP.

I. The medicine and what it is used for

SUBUTEX prolonged-release injection is authorised as therapy for opioid dependence as part of a programme comprising medical, social and psychological treatment. SUBUTEX prolonged-release injection is indicated in adults aged 18 years and older who have agreed to be treated for opioid addiction (see SmPC for the full indication). It contains buprenorphine as the active substance and it is given by subcutaneous injection.

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

Important risks of SUBUTEX prolonged-release injection, together with measures to minimise such 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 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 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*.

II.A List of important risks and missing information

Important risks of SUBUTEX prolonged-release injection are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can

be safely administered. 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 SUBUTEX prolonged-release injection. 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);

List of important risks and missing information	
Important identified risks	hepatitis, hepatic events, use in patients with hepatic impairment drug withdrawal syndrome including neonatal withdrawal
Important potential risks	none
Missing information	use in children/adolescents (< 18 years old)

II.B Summary of important risks

Important identified risk: Hepatitis, hepatic events, use in patients with hepatic impairment	
Evidence for linking the risk to the medicine	Cases of acute hepatic injury have been reported in opioid dependent patients, both in clinical trials and in post-marketing adverse reaction reports following the use of sublingual buprenorphine. The effect of hepatic impairment on the pharmacokinetics (PK) of sublingual buprenorphine has been evaluated in a PK study in which plasma levels were found to be higher for buprenorphine in subjects with moderate to severe hepatic impairment.
Risk factors and risk groups	Patients with viral hepatitis or existing liver dysfunction are at greater risk of liver injury.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.2, 4.3, 4.4 and Instructions for Use (IFU)* *PL sections 2 and 4* Additional risk minimisation measures *None*

Important identified risk: Drug withdrawal syndrome including neonatal withdrawal	
Evidence for linking the risk to the medicine	In patients presenting with marked drug dependence, initial administration of buprenorphine can produce a drug withdrawal syndrome similar to that associated with naloxone. Neonatal withdrawal is an expected and treatable outcome of prolonged use of opioids during pregnancy, whether that use is

	medically-authorised or illicit. Neonatal withdrawal has been reported in infants of women treated with buprenorphine during pregnancy.
Risk factors and risk groups	Withdrawal can occur upon discontinuation, sub-optimal dosing and treatment initiation with transmucosal buprenorphine before objective and clear signs of withdrawal are evident.
Risk minimisation measures	Routine risk minimisation measures *SmPC sections 4.4 and 4.6* *PL section 2, 3 and 4* Additional risk minimisation measures *None*

Missing information: Use in children/adolescents (<18 years old)	
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.2 and 4.4* Additional risk minimisation measures *None*

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 SUBUTEX prolonged-release injection.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for SUBUTEX prolonged-release injection.