Part VI: Summary of the risk management plan

Summary of risk management plan for Buvidal (buprenorphine)

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

The summary of product characteristics (SmPC) for Buvidal and its package leaflet (PL) give essential information to healthcare professionals and patients on how Buvidal should be used.

This summary of the RMP for Buvidal 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 the RMP for Buvidal.

I. The medicine and what it is used for

Buvidal is authorised for treatment of opioid dependence within a framework of medical, social and psychological treatment. Buvidal is intended for use in adults and adolescents aged 16 years or over (see SmPC for the full indication). It contains buprenorphine as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of the benefits of Buvidal can be found in the Buvidal EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

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

Important risks of Buvidal, together with measures to minimise such risks for learning more about the risks of Buvidal, 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 PL 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, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks

Important risks of Buvidal 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 Buvidal. 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.

List of important risks and missing information	
Important identified risks	Injection site reactions Use in patients with severe respiratory insufficiency Use in patients with severe hepatic impairment Use in patients with acute alcoholism or delirium tremens Abuse and misuse Withdrawal reactions in opioid-dependent patients Concomitant use of other medications (Cytochrome P 3A4 [CYP3A4] inhibitors; benzodiazepines; other central nervous system depressants; monoamine oxidase inhibitors [MAOI]; and serotonergic medicinal products) Overdose
Important potential risks	Intravascular injection Medication error Use in patients with various disease states (renal impairment; head injuries; increased intracranial pressure; hypotension; prostatic hypertrophy; and urethral stenosis) Concomitant use of gabapentinoids
Missing information	Use in pregnancy

II.B Summary of important risks

Important identified risk: Injection site reactions	
Evidence for linking the risk to the medicine	Based on safety data collected during the clinical development programme, mild to moderate injection site reactions were commonly observed. The majority of all injection site reactions reported post-marketing are non-serious. However, a few serious, reactions of injection site ulceration, injection site necrosis and

	injection site abscess have been reported post-marketing. However, injection site reactions are not considered to impact the risk-benefit balance of the product, as adverse reactions are mostly mild to moderate and transient. Injection site reactions could potentially be minimised by using the correct administration technique, as described in the SmPC for Buvidal and ensuring that the product is not injected intradermally.
Risk factors and risk groups	No risk factors or risk groups for injection site reactions have been identified for Buvidal.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 6.6 and PL Instructions for use* Additional risk minimisation measures *None*

Important identified risk: Use in patients with severe respiratory insufficiency	
Evidence for linking the risk to the medicine	The increased risk of respiratory depression with buprenorphine is described in scientific literature, but clinically less significant compared to other full agonist opioids, due to the partial agonist properties of buprenorphine. It is logical to assume this risk would be increased in patients with severe underlying respiratory insufficiency.
Risk factors and risk groups	Patients with severe respiratory insufficiency or patients at risk of CNS depression, e.g. taking large quantities of alcohol or taking benzodiazepines for alcohol withdrawal.
Risk minimisation measures	Routine risk minimisation measures *SmPC sections 4.3 and 4.4* *PL sections 2 and 4* Additional risk minimisation measures *None*

Important identified risk: Use in patients with severe hepatic impairment	
Evidence for linking the risk to the medicine	The effects of hepatic impairment on the pharmacokinetics of buprenorphine were evaluated in a post-marketing study of another buprenorphine product. Plasma levels of buprenorphine were found to be higher in patients with moderate and severe hepatic impairment in that study.

Risk factors and risk groups	Patients with moderate to severe hepatic impairment could be at increased risk.
Risk minimisation measures	Routine risk minimisation measures *SmPC sections 4.3 and 4.4* *PL section 2* Additional risk minimisation measures *None*

Important identified risk: Use in patients with acute alcoholism or delirium tremens	
Evidence for linking the risk to the medicine	Buprenorphine-related deaths in patients on opioid agonist therapy have occurred when buprenorphine was taken in combination with other substances, especially alcohol
Risk factors and risk groups	Patients with history of alcohol abuse.
Risk minimisation measures	Routine risk minimisation measures *SmPC sections 4.3 and 4.5* *PL section 2* Additional risk minimisation measures *None*

Important identified risk: Abuse and misuse	
Evidence for linking the risk to the medicine	Product misuse, abuse, and diversion are considered important risks for other buprenorphine products.
Risk factors and risk groups	All patients previously dependent on illicit opioids.
Risk minimisation measures	Routine risk minimisation measures *SmPC sections 4.2 and 4.4* Legal status: *The product is being submitted under special medical prescription in accordance with Article 71 of Directive 2001/83/EC.* Additional risk minimisation measures *None*

Important identified risk: Withdrawal reactions in opioid-dependent patients	
Evidence for linking the risk to the medicine	The risk of precipitated withdrawal is a known risk of the reference product.

Risk factors and risk groups	Patients are at risk of withdrawal reactions at initiation of Buvidal treatment.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.4* *PL section 2* Additional risk minimisation measures *None*

Important identified risk: Concomitant use of other medications (Cytochrome P 3A4 [CYP3A4] inhibitors; benzodiazepines; other central nervous system depressants; and monoamine oxidase inhibitors [MAOI]; and serotonergic medicinal products)	
Evidence for linking the risk to the medicine	Based on the knowledge of use of other buprenorphine products, buprenorphine should not be taken together with alcohol and should be used cautiously together with benzodiazepines, other CNS depressants, opioid analgesics, naltrexone, MAOI, serotonergic medicinal products, and CYP3A4 inhibitors and inducers.
Risk factors and risk groups	Patients with HIV (receiving protease inhibitors like ritonavir, nelfinavir or indinavir, which are CYP3A4 inhibitors); patients with fungal infections (receiving azole antifungals); patients with anxiety or other psychiatric disorders receiving benzodiazepines, certain antidepressants, MAOI, serotonergic medicinal products, or neuroleptics; patients with allergic disorders receiving sedative H1-receptor antagonists; patients with acute or chronic pain treated with certain analgesics that lead to CNS depression. All patients receiving multiple concomitant medications, such as severely ill or elderly.
Risk minimisation measures	Routine risk minimisation measures *SmPC sections 4.4 and 4.5* *PL section 2* Additional risk minimisation measures *None*

Important identified risk: Overdose	
Evidence for linking the risk to the medicine	From the current knowledge on buprenorphine and Buvidal, it is anticipated that the risk of overdose (associated primarily with respiratory depression) is lower with buprenorphine (which is an opioid partial agonist/antagonist) than with full agonist opioid agents and will be even lower with this formulation compared to

	sublingual buprenorphine formulations, as Buvidal will be administration by healthcare professionals only.
Risk factors and risk groups	The risk of serious adverse events such as overdose is greater if the patient is under-treated with buprenorphine and continues to self-medicate with opioids, alcohol or other sedatives and hypnotics (in particular benzodiazepines) in order to prevent withdrawal symptoms.
Risk minimisation measures	Routine risk minimisation measures *SmPC sections 4.4, 4.5 and 4.9* *PL sections 2 and 4* Additional risk minimisation measures *None*

Important potential risk: Intravascular injection	
Evidence for linking the risk to the medicine	There is currently no data with regards to accidental intravascular administration of this product in humans.
Risk factors and risk groups	Product use outside of the recommended healthcare setting, or by inexperienced staff. Product abuse or misuse.
Risk minimisation measures	Routine risk minimisation measures *SmPC sections 4.2, 4.4, and 6.6* *PL Instructions for use* Additional risk minimisation measures *None*

Important potential risk: Medication error	
Evidence for linking the risk to the medicine	There is currently no evidence of such use.
Risk factors and risk groups	Product use outside of the recommended healthcare setting, or by inexperienced staff.
Risk minimisation measures	Routine risk minimisation measures *SmPC sections 4.2 and 4.4* *PL section 3* Other routine risk minimisation measures beyond the Product Information: The product is intended to be administered by healthcare professionals only. The secondary packaging for weekly and monthly products will be in different colours. In addition, the

	different doses will be differentiated by different colours on the secondary packaging. Additional risk minimisation measures *None*
Important potential risk: Use in patients with various disease states (renal impairment; head injuries; increased intracranial pressure; hypotension; prostatic hypertrophy; and urethral stenosis)	
Evidence for linking the risk to the medicine	Opioids may elevate cerebrospinal fluid pressure and should be used with caution in patients with head injury, intracranial lesions, other circumstances where cerebrospinal pressure may be increased, or in patients with a history of seizure. Opioids have been shown to increase intracholedochal pressure. Buprenorphine as an opioid should therefore be used with caution in patients with dysfunction of the biliary tract.
Risk factors and risk groups	Patients with these various (underlying) disease states (renal impairment; head injuries; increased intracranial pressure; hypotension; prostatic hypertrophy; and urethral stenosis).
Risk minimisation measures	Routine risk minimisation measures *SmPC sections 4.2 and 4.4* *PL section 2* Additional risk minimisation measures *None*

Important potential risk: Concomitant use of gabapentinoids	
Evidence for linking the risk to the medicine	There have been reports of gabapentinoids being misused, with subsequent development of dependence, in particular in patients with opioid dependence. The concomitant use of pregabalin or gabapentin and opioids are of concern as the respiratory depressive effects might be exacerbated and increase the risk for overdose deaths.
Risk factors and risk groups	Patients with anxiety or other psychiatric disorders, epilepsy, or neuropathic pain receiving treatment with gabapentinoids for these indications, or patients misusing gabapentinoids.
Risk minimisation measures	Routine risk minimisation measures *SmPC sections 4.4 and 4.5* *PL section 2* Additional risk minimisation measures *None*

Missing information: Use in pregnancy	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.6* *PL section 2* 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 Buvidal.

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

There are no studies required for Buvidal.