

Part VI: Summary of the risk management plan

Summary of risk management plan for Buprenorphine

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

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

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

I The medicine and what it is used for

Buprenorphine transdermal patch is authorised for treatment of non-malignant pain of moderate intensity when an opioid is necessary for obtaining adequate analgesia (see SmPC for the full indication). It contains buprenorphine as the active substance and it is given by the transdermal administration route in the form of a patch supplied in the following strengths: 5, 7.5, 10, 15, 20, 25, 30 and 40 microgram/hour.

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

Important risks of buprenorphine, together with measures to minimise such risks and the proposed studies for learning more about buprenorphine's risks, are outlined below.

Measures to minimise the risks identified for medicinal products are:

- 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 medicine is supplied to the patient with prescription only 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 buprenorphine is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of buprenorphine 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 buprenorphine. 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	Respiratory depression Accidental overdose Drug withdrawal Drug abuse and dependence
Important potential risks	Medication error
Missing information	Use in pregnant or breastfeeding patients Paediatric use

II.B Summary of important risks

Important identified risk - Respiratory depression	
Evidence for linking the risk to the medicine	Respiratory depression (usually presented as shallow and weak breathing) is a class effect for opioids and is one of the major causes for mortality associated with opioid use. The primary mechanism involves a reduction in the responsiveness of the brainstem respiratory centres to carbon dioxide. The frequency of respiratory depression based on the clinical data for BTDS is rare ($\geq 0.01\%$ to $< 0.1\%$), but the reaction may be a life-threatening medical emergency, requiring specific treatment. Inclusion of this risk is supported by evidence drawn from the published literature, clinical trial experience and post-marketing safety data.
Risk factors and risk groups	Use in opioid naive patients Subsequent to overdose Subsequent to drug abuse Use in patients with pre-existing respiratory disorders chronic obstructive pulmonary disease, lung disorder, lung neoplasm, asthma, cerebellum infarction, severe cerebral palsy, sleep apnoea syndrome
Risk minimisation measures	Routine risk minimisation measures Routine risk communication is present in the following sections:

	<p>- SmPC:</p> <ul style="list-style-type: none"> • Section 4.4 • Section 4.5 • Section 4.6 • Section 4.8 • Section 4.9 <p>- PL section:</p> <ul style="list-style-type: none"> • Statement in the introduction of the PL • Section 2 • Section 3 • Section 4 <p>Risk minimisation activities in the Product Information beyond routine risk communication:</p> <p>Risk minimisation activities in the Product Information beyond routine risk communication:</p> <ul style="list-style-type: none"> - SmPC section 4.3 contraindication for patients with conditions in which the respiratory centre and function are severely impaired or may become so - SmPC in section 4.9 treatment recommendation is present - Statement in the introduction of the PL to take the patch off and seek medical help if breathing becomes shallow and weak <p>Additional risk minimisation measures</p> <p>None</p>
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Important identified risk - Accidental overdose	
Evidence for linking the risk to the medicine	<p>Opioid overdose is associated with high mortality rate, which is usually presented with decreased level of consciousness (starting as feeling very sleepy and progressing to loss of consciousness) and respiratory depression (presented as shallow and weak breathing). Accidental overdose with buprenorphine can be caused by inappropriate drug administration (such as taking a higher dose in error), or to other factors, including increased absorption from the patch due to heat exposure, or reduced rate of elimination from the body due to liver or kidney disorders. The most serious complication is significant respiratory depression including apnoea (cessation of breathing). Such situations are medical emergency and require immediate medical intervention in a hospital setting. Inclusion of this risk is supported by evidence drawn from the post-marketing safety data.</p>
Risk factors and risk groups	<p>Use in patients with severe hepatic impairment reducing clearance of the drug, which may lead to an increase in plasma concentration</p> <p>Use in patients co-administered BTDS and drugs that reduce the clearance of the drug, which leads to an increase in plasma concentration</p> <p>Subsequent to drug abuse or dependence (17.2% of the cases occurred subsequent to drug abuse, dependence or in patient with a history of drug abuse or dependence)</p> <p>Subsequent to medication errors (23.0% of the cases occurred</p>

	subsequent to medication error)
Risk minimisation measures	<p>Routine risk minimisation measures:</p> <p>- SmPC:</p> <ul style="list-style-type: none"> • Section 4.2 • Section 4.4 • Section 4.9 <p>- PL section:</p> <ul style="list-style-type: none"> • Statement included in the introduction of the PL • Section 3 <p>Risk minimisation activities in the Product Information beyond routine risk communication:</p> <ul style="list-style-type: none"> - Section 4.2 of SmPC: Advice for titration and monitoring - Section 4.2 of SmPC: Advice for use in patients with hepatic impairment and that they need to be monitored - Section 4.2 of SmPC: Advice for use in patients with fever or exposed to external heat and the risk of increased absorption - Section 4.9 of SmPC treatment recommendation is present for overdose - Section 3 of PL: Advice to remove all patches and call the doctor or hospital

Important identified risk - Drug withdrawal	
Evidence for linking the risk to the medicine	Withdrawal syndrome (also known as "abstinence syndrome") is a well-known effect for the entire opioid class, which may be serious and require urgent medical attention. The symptoms develop after abrupt cessation (or dose decrease), and typically include effects, opposite to the main pharmacological action of opioids. Inclusion of this risk is supported by evidence drawn from the published scientific data, clinical trial experience and the post-marketing safety data.
Risk factors and risk groups	Risk factors include socio-demographic factors, pain and drug-related factors, genetics, environment, psychosocial and family history, and alcohol and substance use disorders, prolonged opioid use or patients who abruptly cease therapy (more than 90 days BTDS therapy), subsequent to medication error affecting the absorption rate of buprenorphine, subsequent to product quality error i.e. adhesion issue, patch malfunction resulting in abrupt withdrawal of buprenorphine.
Risk minimisation measures	<p>Routine risk minimisation measures:</p> <p>- SmPC:</p> <ul style="list-style-type: none"> • Section 4.3 • Section 4.4 • Section 4.6 • Section 4.8 <p>- PL section:</p> <ul style="list-style-type: none"> • Section 2 • Section 3 • Section 4 <p>Risk minimisation activities in the Product Information beyond</p>

	routine risk communication: - Section 3 of PL: Advice to contact treating doctor if symptoms appear after stop using patches
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Important Identified Risks - Drug abuse and dependence	
Evidence for linking the risk to the medicine	<p>Opioid abuse and dependence have been recognized as a serious problem with various implications which spread outside the individual patient's physical and mental health. Apart from serious medical problems, the individuals' social and economic status may be affected with an inability to retain a job and changes in relationships with family and friends. The potential impact on public health may be substantial. Although buprenorphine is a partial agonist, and the transdermal formulation is unlikely to be attractive for drug abuse, the potential for such cannot be adequately characterized during controlled trials and therefore requires further attention. Inclusion of this risk is supported by evidence drawn from the published literature and post-marketing safety data.</p>
Risk factors and risk groups	<p>Risk factors include socio-demographic factors, pain and drug-related factors, genetics, environment, psychosocial and family history and alcohol and substance use disorders</p>
Risk minimisation measures	<p>Routine risk minimisation measures:</p> <p>- SmPC:</p> <ul style="list-style-type: none"> • Section 4.3 Contraindication • Section 4.4 Special warning and precaution for use • Section 4.8 Undesirable effects <p>- PL section:</p> <ul style="list-style-type: none"> • Section 2 • Section 4 <p>Risk minimisation activities in the Product Information beyond routine risk communication:</p> <p>None</p> <p>Other risk minimisation measures beyond the Product Information:</p> <p>Classification as a Controlled Drug. This restrictive classification raises the overall level of vigilance and surveillance</p> <p>Restricting prescribers: a prescription is required before buprenorphine can be obtained.</p>

Important Potential Risks - Medication error	
Evidence for linking the risk to the medicine	<p>Errors associated with the use of medicinal products may present a significant public health concern due to their versatile nature and the associated difficulties in prediction/estimation of their occurrence. As they are unintended acts, occurring at various stages of the clinical practice, an adequate assessment of the potential for medication error is very difficult during the clinical trial phase. Since medication error</p>

	may lead to clinically significant outcomes (such as accidental overdose), and proper monitoring and evaluation of error patterns may increase the preventability of error via appropriate measures in labelling, medication error is considered as important potential risk. Inclusion of this risk is supported by evidence drawn from the published literature, clinical trial experience and post-marketing safety data.
Risk factors and risk groups	Patients with cognitive impairment Patients undergoing opioid rotation from a different transdermal opioid Patients commencing BTDS therapy
Risk minimisation measures	Routine risk minimisation measures: <ul style="list-style-type: none"> - SmPC: <ul style="list-style-type: none"> • Section 4.2 - PL section: <ul style="list-style-type: none"> • Section 3 Risk minimisation activities in the Product Information beyond routine risk communication: <ul style="list-style-type: none"> - Advice for titration and monitoring is present in section 4.2 of SmPC - Advice is present in section 3 of PL of what to do when more or less medication applied

Missing Information - Use in pregnant or breastfeeding patients	
Risk minimisation measures	Routine risk minimisation measures: <ul style="list-style-type: none"> - SmPC: <ul style="list-style-type: none"> • Section 4.6 • Section 4.8 - PL section: <ul style="list-style-type: none"> • Section 2 • Section 4 Risk minimisation activities in the Product Information beyond routine risk communication: None

Missing Information - Paediatric use	
Risk minimisation measures	Routine risk minimisation measures: <ul style="list-style-type: none"> - SmPC: <ul style="list-style-type: none"> • Section 4.2 Posology and method of administration - PL section: <ul style="list-style-type: none"> • Section 2 Risk minimisation activities in the Product Information beyond routine risk communication: None

II.C Post-authorisation development plan

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

There are no studies that are conditions of the marketing authorisation or specific obligation of BTDS.

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

There are no studies required for buprenorphine.